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INTERNAL MEDICINE

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Restrictions Imposed on Antibiotic Therapy by Renal Failure

Calvin M. Kunin and Maxwell Finland

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A. M. A.
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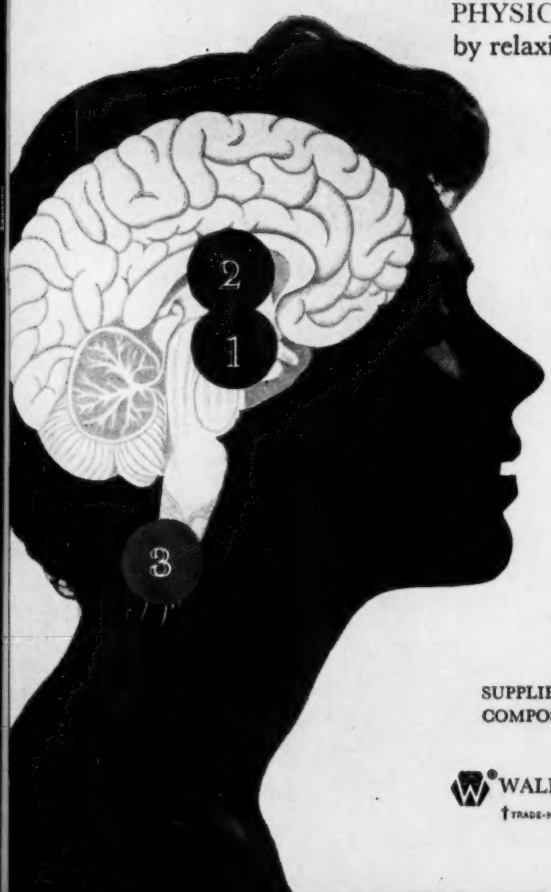

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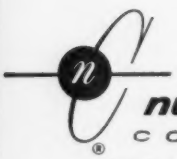

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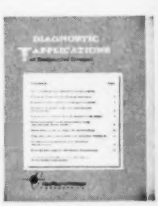

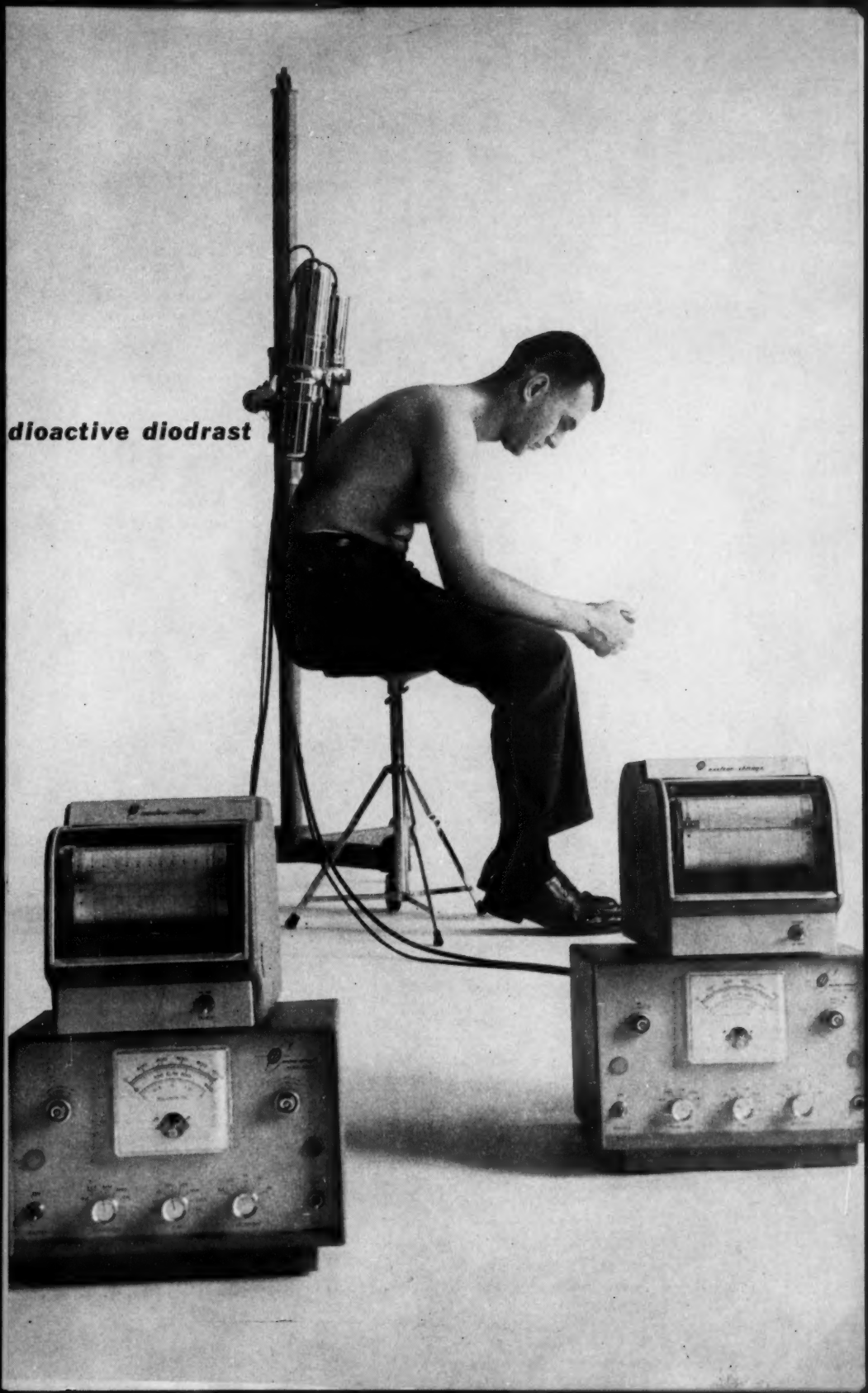
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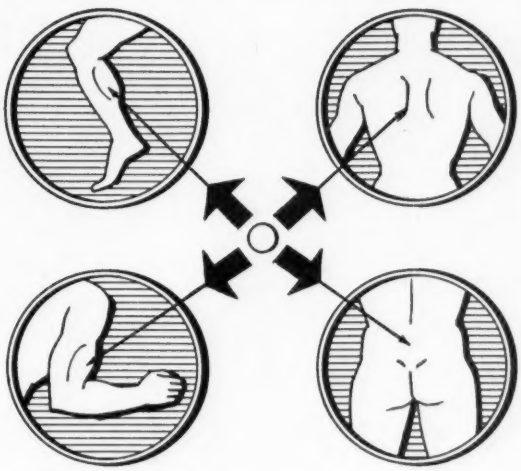

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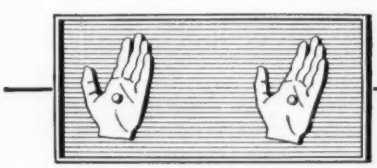

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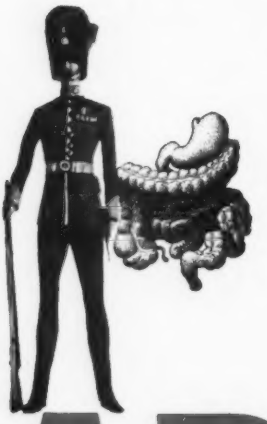

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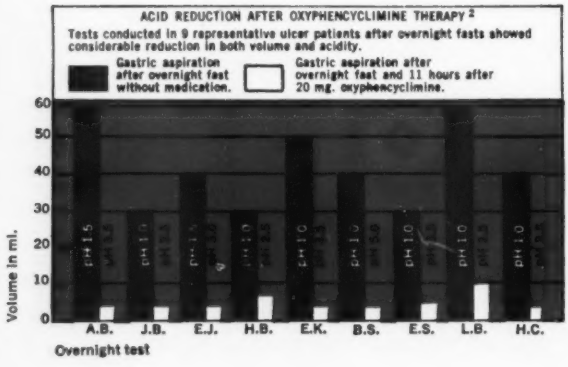

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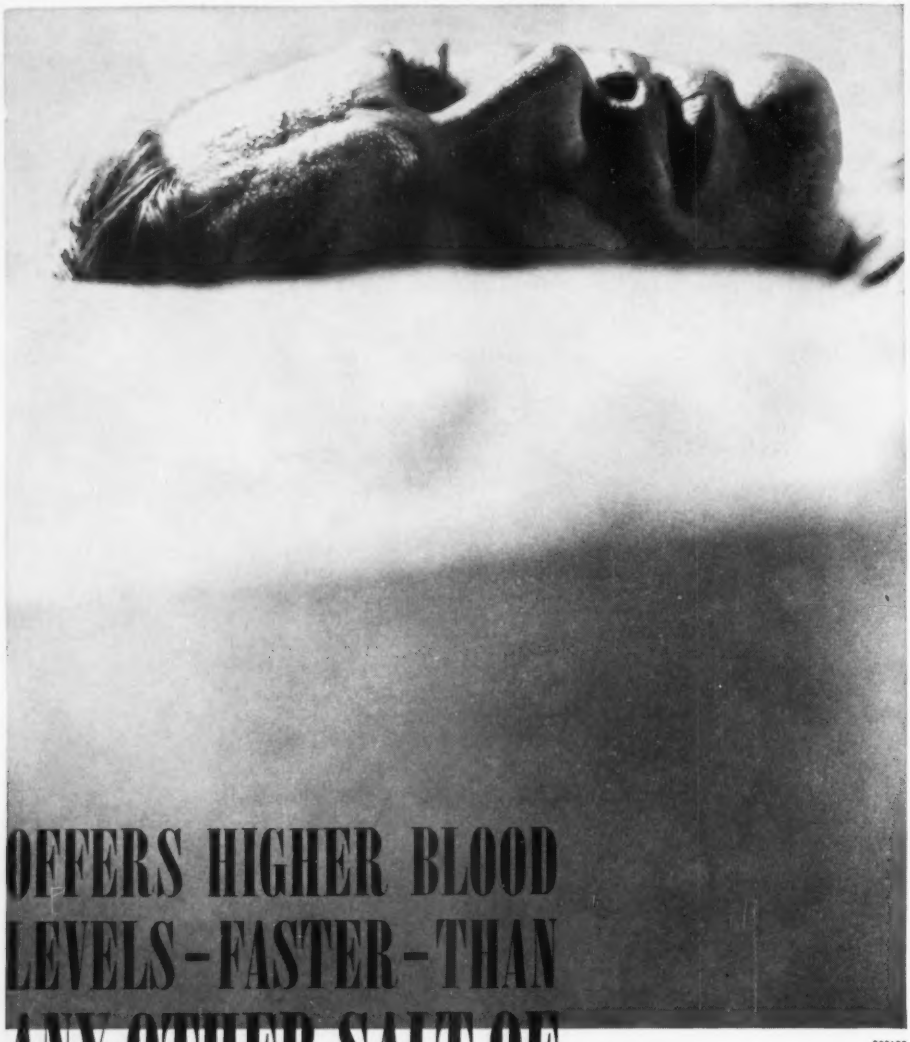

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Editorials

Needed: More Emphasis on Disease Prevention in Internal Medicine

Preventive medicine is currently defined[1] as the science and art of preventing disease, prolonging life, and promoting physical and mental health and efficiency. Such objectives are rightfully an integral part of the practice of internal medicine, but few would deny that preventive measures tend to be displaced by the more strictly curative efforts of the busy practitioner.

The ounce of prevention is too often overshadowed by the pound of cure. The unhappy results of this imbalance are found in medical wards, clinics, and physicians' offices everywhere. Examples include not only such obvious instances as the unvaccinated young adult with paralytic polio and the grossly overweight diabetic but also the patient with chronic pulmonary disease whose earlier asthmatic state was inadequately treated, the person with advanced rheumatic carditis who escaped proper prophylaxis, the peptic ulcer patient whose behavior invited recurrence and complication, the cirrhotic who could have been salvaged by aggressive therapy during the early stage of the disease, and the chronic nephritic progressing inexorably to an early uremic or hypertensive death without benefit of constructive management. In many instances, the presence of such cases indicates failure of a program of disease prevention. The responsibility for this neglect of preventive practice lies with both the patient and the physician.

There comes to mind the problem patient who, although told of measures necessary for the preservation of health, refuses to follow advice. Such behavior is discouraging and frustrating to the physician. Fortunately, this experience is more the exception than the rule. Follow-up studies of preventive and constructive medicine programs generally show high levels of patient cooperation. Certainly, failure of the patient to carry out medical instruction in no way relieves the physician of the responsibility of offering and encouraging health practices of the highest professional level at his command.

It is said that adults in America are not interested in preventive measures for personal health; that they fail to cooperate with programs designed to prevent communicable diseases (poliomyelitis, tetanus, typhoid), or to detect conditions during early, asymptomatic stages (tuberculosis, cancer, diabetes); that they will consult a physician only in the presence of established illness. These accusations tend to be refuted by the numerous occasions when examinations or other health activities are routinely accepted by persons in apparent good health. At work, pre-

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placement "physicals" are increasingly commonplace, and whenever periodic health inventories are offered, employees accept both willingly and gratefully. Millions have regularly scheduled dental check-ups. Certain fraternal and social organizations require certification of good health. Examinations related to military service are conducted on a large segment of our population each year. Premarital examinations, while varying tremendously in completeness, are, nevertheless, required in all states. Admission to most universities, colleges, and public schools is dependent on medical examination, as is participation in many amateur and professional sports. The growth and development of infants and children are observed by pediatricians at "well baby" clinics, where visits take place without regard to the existence of sickness. Further, a major portion of the obstetrician's work is directed toward the prevention of disease in mother and fetus. Thus, it would seem that most people actually have a considerable background of conditioning in medical examinations and health activities unrelated to the presence of active disease. Can one really say that they are not receptive to preventive medicine practices? Why can't patients, with encouragement and education, learn to appreciate the value of preventive health measures?

Physicians are often ill-prepared for optimal use of the techniques of preventive medicine. In medical school curricula the traditional emphasis has been on teaching the morbid processes of disease. It is not surprising that medical students, interns, and residents may show little interest in maintaining health in well persons and the early detection of disease in near-normal patients. In practice, physicians tend to devote more and more time to *therapeutic* (in contrast to *preventive*) medical activities. Such limitation in the scope of medical practice is, of course, contrary to the trend toward comprehensive medical care which exists today.

Enlightened medical educators are meeting the challenge by presenting the principles of preventive medicine in a stimulating manner at all levels of professional training. Important roles are played by epidemiologists, public health specialists, biostatisticians, and research workers in demonstrating the value of disease prevention in medicine. Among all practitioners, the internist is particularly well suited for the adoption of preventive techniques in the everyday management of the patient.

Concerned with "the most all-inclusive of the specialties," [2] the internist has the depth of interest essential for the practice of truly comprehensive medicine. He has the inquisitiveness to follow-up each suggestive lead from history or examination which may result in the detection of disease at the earliest possible moment. His diagnostic know-how establishes complete and correct diagnoses. He has learned patience in the continuing management of long-term illness. He has developed therapeutic skills necessary to minimize disability resulting from those conditions which cannot be aborted or corrected. He has the flexibility, experience, and judgment needed for the adoption of new methods and ideas.

Research, both in the basic sciences and at the clinical level, has created a dazzling new armamentarium for the physician's use in the management of disease. New antibiotics, steroids, antihistamines, ataractics, diuretics, and antihypertensive medications are included in the list of effective therapeutic agents developed during the last decade. Proper application directs their use for the prevention of disease and disability, not merely for the alleviation of symptoms in advanced pathologic states. And wonderful advances are forthcoming. A broad-spectrum vaccine to prevent respiratory disease and agents to control atherosclerosis and neoplasm are opti-

mistically predicted. What amazing implications for disease prevention the future holds!

The era of total, comprehensive medical care demands full utilization of preventive health measures. The internist should lead the way in the reorientation of medical practice so as to give preventive medicine the emphasis it deserves.

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Changing Trends in Clinical Investigation

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Changing trends in American medicine, medical education, and research have for many years been favorite subjects for messages from chairmen. Nevertheless, since this represents the Centennial Meeting of the Section on Experimental Medicine and Therapeutics, it seems timely to discuss briefly a few of the problems related to the dynamic developments in science in terms of their impact on clinical investigation.

The word "clinical" is derived from the Greek word *klinikos* which means bed; hence, Dr. Fuller Albright pointed out 15 years ago, "Since animals do not sleep in beds, it is quite clear that 'clinical investigation' has primarily to do with the investigation of sick people and is concerned only secondarily, if at all, with sick laboratory animals." [1] One could argue the restrictions imposed by the above statement. Few would disagree that the greatest contributions from clinical investigation have come from success in opening up new knowledge of mechanisms, diagnosis, and treatment of disease in human beings.

Opportunities in clinical research are greater than ever before. Money is relatively plentiful; new institutions have been developed, and the old ones have increased in size. There are many indications that there will be more opportunities for capable men in the future. Yet these developments have created a series of problems which all who are concerned with the vital responsibility of fostering and maintaining productive clinical research must face. Clearly, the primary responsibility will continue to be that of stimulating and recruiting to clinical investigation men with fertile minds who are motivated for research. However, there is little question that recruitment of such men to clinical medicine will increasingly involve competition with many other fields of science.

The astonishing advances in all of the physical and natural sciences have created a peculiarly difficult dilemma for the clinical investigator. He recognizes the unassailable fact that progress in clinical medicine has resulted almost without exception because of previous advances in knowledge in the basic biological, physical, and—more recently—social sciences. As medicine has become more and more a precise science, it has become imperative that the clinical investigator obtain a sound knowledge of these basic sciences. It is a common experience for a resident, having completed a long and arduous course of training in clinical medicine, to feel inadequately prepared for a career in clinical investigation (however good his medical school basic science education may have been). Hence, he embarks upon further extensive training in a variety of basic sciences, such as chemistry, nuclear physics, or genetics. Yet this resident is usually well past 30 years of age, beyond the period during which many men, in all fields of endeavor, have historically made their greatest contribution. The difficult decisions he must make reemphasize the need for hard, critical, and continuing examination of the efficiency of all phases of our American educational system.

This need for further basic scientific training is being met in a number of ways. In many clinical research centers biochem-

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ists or physicists have joined the clinical groups. Although the presence of such men in daily working proximity does not lessen the necessity for the clinician to understand the major principles of the basic sciences represented, they can provide for him one means by which he can acquire significant basic principles and facts at the same time he is pursuing the clinical problems which challenge him. Were this movement of basic scientists into clinical groups to proceed at a pace which would seriously diminish the number of persons working primarily in their own discipline, it could create an undesirable effect on the basic sciences from which they come. On the other hand, the increasing number of basic scientists participating in clinical fields demonstrates the fortunate recognition that investigation in clinical departments is rapidly becoming inseparable from that carried out in all areas of biological inquiry. A similar intermingling of learning is evident where, either by design or spontaneously, joint or interdisciplinary groups have developed. In these the members, while retaining their own departmental status, are attacking problems utilizing their combined capabilities. The provision of additional individual training in a basic science laboratory may best fit some men's needs, recognizing the adverse influence of prolonging training mentioned above. A possible favorable by-product of return of the clinically trained men to basic science laboratories could be that some of them would elect to remain in the basic discipline. The loss to clinical investigation would be a gain to the basic medical sciences where recruitment, at least in some areas, is becoming increasingly difficult.

Reference has been made to the place of animal experimentation in clinical investigation. Should clinical investigators, stimulated by observations on patients, undertake to answer questions by means of well-planned experiments in animals? From one point of view, it could be argued that the clinical investigator should limit his activities to the study of sick people and attempt to persuade his colleagues in the basic sciences to carry out the animal experiments. In practice, except for the occasional fortunate blending of interests in a given institution, this is impractical. I would strongly oppose any such limitation for several reasons. First and most important, such a policy is opposed to scientific principle; the true investigator seeks answers to his questions by using any and all means and techniques available to him. Second, society—scientists and laymen alike—has become increasingly concerned with the perplexity of the legal, ethical, and moral aspects of human experimentation since the terrible events of World War II. The proper place of human experimentation poses a difficult and complex problem for which there is no easy answer.[2] In the context of this discussion, I would submit that uneasiness about the extent to which the human should be the experimental subject is undeniably one reason why one finds in most clinical research centers many more rats and dogs than was true a generation ago. Third—but related to both of the above points—many questions originating at the bedside can be more quickly and accurately answered, at least as applied to the animal species used, by carefully planned and controlled animal experiments than by study of the patient. Some experiments on humans are completely impossible; in others they are indecisive, and in many there is anxiety over the degree of hazard to patients or subjects under study. The recent work of Welt, Oliver, Hollander, Williams, Winters, and others, which clarifies the renal structural and functional lesions of potassium depletion as observed in the rat, provide an example of the precision which is possible by utilization of animal experiments to help answer an important clinical question.[3,4]

Hence, it seems certain that clinical investigation should and will become more closely associated with the rapid developments in all of the basic sciences. This prediction, however, carries with it certain

implications as far as clinical research is concerned. The clinical investigator should remind himself periodically that his primary goals are related to the better understanding and treatment of sick people. The approach is less important than the goal. Solution of a problem may involve moving a great distance from the bedside; if, however, the investigator's activities are in an orbit which eventually provides a better understanding of the original clinical question, I would propose that all phases of his endeavor are clinical investigation. Some persons traversing the orbit may find they can make a greater contribution if they stop permanently at some point removed from the clinic or bedside. Until they make that decision, however, it would appear imperative to the writer that they keep their clinical skills sharpened by continuing and regular association with, and responsibility for, patients on the ward and in the clinic. The speed with which their investigation proceeds may not be as rapid as it would be if they dropped their clinical responsibilities, but the unanswered questions in human illness will inevitably be kept in sharper focus. At the same time, too much patient care and clinical teaching responsibility can and does inhibit the productiveness of many clinical investigators. The provision of adequate time and facilities for the competent investigator is a goal which chairmen of most of the clinical departments in medical schools in the United States continually strive for but rarely reach satisfactorily. Similarly, a chairman's attempts to apportion assignments in order to meet all of the pressing service, educational, and research needs of his particular department are usually only partially successful. Clearly, neither unlimited laboratory space nor funds can insure good clinical research; nonetheless, more of both in liberal quantities will help medicine meet the challenge of keeping up with the growing pace of clinical investigation. The relationship of these needs to medical education and care is self-evident. Unless an atmosphere conducive to continued and productive investigation is provided, the quality of medical education must inevitably degenerate.

In summary, although this is an era in which the potential for the further development of experimental medicine and therapeutics is the greatest in history, the full exploitation of this potential will require solution of many problems, a few of which have been discussed here.

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The Endeavor of Internal Medicine, 1859-1959

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An architect intent upon his drawing board and blue-prints at times must back away from the minutiae, stand off, and let his fancy soar. On this centennial occasion let us look up from our myopic concern with the things of the moment and consider the design and structure of internal medicine in America over the past hundred years, the present, and the future into which we are flowing on the inexorable tides of time.

The occasion of celebrating the 100th birthday of what is now the Section on Internal Medicine of the American Medical Association sets the stage for review, view, and preview. Americans, having no official royalty or nobility, miss the pageantry of celebrations of the old world where numerous institutions have marked many a hundred-year notch on the long calendars of their antiquity. A democracy with more pliable forms responds very rapidly to the forces which shape society. History changes daily before our eyes. Medicine and science hold a preeminent place in the imagination of contemporary man. How did this come about? How may this prestige be used for the general good? What will cause it to wither?

Advances in medicine are based on teaching and research. These functions are discharged in schools of medicine. They have followed different patterns in different countries. The great medical schools of Britain arose from hospitals where skill in the arts of medicine made the natural history of disease a medium for humanistic learning and belles-lettres. French medical schools also arose as appendages of hospitals. When German universities emerged from the cloud cover of heavy Romanticism and mysticism, the medical school was there as an integral part of the university, an organ of the state. American schools too often were backwoods improvisations or proprietary business ventures. Doctors, if they could, salvaged the victims of scalp wounds or spoiled food, or those sick with the plagues resulting from the conjoint sewage and water systems of our cities.

When the A.M.A. began, medicine was a single, almost comprehensible whole. A student cheerfully learned in a brief period the little he was supposed to need for practice. Often he strengthened it by clinical work in a large city hospital. Infections, with their heavy toll of infant deaths, were accepted as part of the scheme of things. Epidemics of cholera and yellow fever varied the theme of typhoid and pneumonia. Except for mercury and quinine, with their narrow spectrum of therapeutic effectiveness, treatment was expectant. The physician was the friend who gave support by his presence and sympathy in the face of death. Medically, life was simple. Therapeutic nihilism was scientific realism, since there was so pitifully little which the doctor could do towards specific cure. Therapy was aimed at symptoms. It did not remove causes. Homeopathy, borne aloft because most minor illness is self-correcting, was tempering the wholesale butchery of Rush's bloodletting and the vast seas of calomel, twin scourges which only our hardiest ancestors survived.

Quacks flourished in the presence of such hopelessness and error. Many a for-

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tune was made from patent medicines with testimonial endorsement of an army of gullible or meritricious clergymen whose theological concentration rendered them unable to realize that *post hoc* could be anything other than *propter hoc*. For each hospital there were hundreds of churches. The curious alliance of free press and nostrum purveyer made the opportunity for the merely literate to be seduced by that day's hucksters. Connivance or ignorant belief in panaceas let ministers of the Gospel shill for patent nostrum makers, the innocent patient victim of a strange conspiracy—priest, huckster, and free-lance newspaper. Alcohol became a genteel beverage for the anti-saloon-leaguer when dispensed as an all-curing herb root. And who is to say that it did not lighten the crushing ennui of small town life in provincial areas?

The American Medical Association was built by men of vision who were concerned with the quacks, the peddlers of nostrums, and other frauds; the deplorable inadequacy of medical education by apprenticeship, and the lack of protection of the public against diploma-mill doctors whose school was only a printing press to manufacture certificates. For the first twelve years of its existence the A.M.A. had only large general meetings. The first forces of specialization were coming into focus. One hundred years ago sections were formed. For a few hours there were only four—Practical Medicine and Obstetrics, Surgery, Anatomy and Physiology, and Chemistry and Materia Medica. But later the same day were added a Section on Meteorology, Medical Topography, and Epidemic Diseases and another on Medical Jurisprudence and Hygiene. From this beginning came the present sections which now represent the diverse interests of physicians of America.

One by-product of our addiction to the decimal system is the custom of celebrating centennials. This arbitrary bracketing by hundreds is artifactitial, for history does not accommodate itself into nice bundles of one hundred years. Nevertheless, a hundred years sweeps the room clean. Among the famous men who died in 1859 were Thomas Babington Macaulay, the historian and essayist; Rufus Choate, the lawyer; Washington Irving, the novelist; Alexander Humboldt, the naturalist, and Henry Hallam, the historian. Of famous people *born* one hundred years ago none is left to tell his story. Henri Bergson, Pierre Curie, Conan Doyle, Lord Curzon, Eleanora Duse, Alfred Dreyfus, Havelock Ellis, A. E. Housman, Knud Hansum, Francis Thompson, and Sidney Webb made their marks and departed. No survivors, not even the indestructable centenarian, can tell us exactly how things were.

So we must rummage in old books to guess what America was like a hundred years ago. Though the cold war of slavery and secession was running out its sands very rapidly, this was not recognized by the man on the street in 1859. Readers were full of talk of the latest Dickens novel, *The Tale of Two Cities*. Other literary and musical works of the year included *The Rubaiyat of Omar Khayyam*, by Edward Fitzgerald; *Adam Bede*, by George Eliot; *The Ordeal of Richard Feverel*, by George Meredith; *The Two Paths*, by John Ruskin; *The Bertrams*, by Anthony Trollope; *Idylls of the King*, by Alfred Tennyson; Gounod's *Faust;* Offenbach's *Orpheus in the Underworld*, and Wagner's *Tristan and Isolde*. Oliver Wendell Holmes, America's most famous physician-author, published *The Professor at the Breakfast Table*.

The ad-men were using the "hard sell" to push their merchandise. Patent medicines loom large in the journal literature of the day. Clergymen of various sorts were versatile and prolific endorsers. The Rev. Henry Ward Beecher, commented as follows: "Bronchitis, clergymen's sore throat —it arises from cold or any unusual exertion of the voice—these incipient symptoms are delayed by using Brown's bronchial troches, which if neglected an entire loss of voice is often experienced. Preeminently

the fi-st and best." The Rev. Dr. Wood described hair restorer in the following glowing terms: "Since using Mrs. S. A. Alan's world hair restorer and zylobalsamum, my hair is greatly thickened. The same is true of my daughter, whose hair came out constantly until we thought her head would be almost bare, but it has handsomely thickened, and has a healthy appearance." The recent cyclical recurrence of the hula-hoop recalls the more firmly ensconced and guarded hoopskirts, the new look, in 1859 such a rage that one New York firm was turning them out at the rate of 10,000 a day, providing work for hundreds of seamstresses at the bountiful stipend of $4 a week. The crime story of the year was that Congressman Daniel E. Sickles, of New York, one Sunday morning in February shot and killed his wife's lover, Phillip Barton Key, son of Francis Scott Key, on a street across from the White House. Details of the shooting, trial, acquittal, and subsequent reconciliation took up much space in the yellow journals of the time. The new game of baseball was beginning to get a grip on customer interest. In Harper's magazine the novice is instructed as follows: "The bat is held high in the air. When the ball has been struck, the 'outs' try to catch it, in which case the striker is out, or, if they cannot do this, to strike the runner with it when he is running which likewise puts him out. Instead of wickets there are at this game four or five marks called bases, one of which being the one at which the striker stands is called home. As in cricket, the point of the game is to make the most runs between those bases; the party which counts the most runs wins the day."

The year 1859 was a memorable one, though it was not that once in a millenium, that *annus mirabilis* so filled with golden days that no one can bear to let it go. At least four major forces which govern our lives today were emerging, though their future influence was hardly suspected.

I. John Brown's raid at Harper's Ferry was the big news of the autumn of 1859. This was looked upon as the work of a half-crazed maniac and discounted by the political pundits. John Stewart Mill wrote *On Liberty*. Near the horizon rumbled the ominous thunder from the sheet-lightning passions forecasting the holocaust of civil war. Dan Emmett, troubadour and minstrel of the period, wrote *Dixie* just in time for it to become the battle hymn of the Confederacy. Even a hundred years have hardly seen the anger of those days cool. The problems of human freedom and equality remain unchanged and unsolved.

II. An idea revolutionizing our whole concept of life crystallized from the massive intellects of Darwin and Wallace. The demonstration that species were not forever rigid and immutable, that man had risen, evolving from a long procession of lower animals, shattered Victorian complacency. It marked a turning point in the pilgrimage of man as he struggles to gain the capacity to look at himself honestly, even at the risk sometimes of making himself smile. Centuries of religious certainty now burst against the hard face of reality, confronting unpalatable but undeniable facts. This milestone, measuring progress, was carved out of the millstone of bigotry and self-deceit which so regularly have encumbered man in his efforts to advance. The reverberations from Darwin's ideas finally died like the last quivering of a snake's tail at sundown in 1925 when William Jennings Bryan bootlessly tried to mix and confuse men and monkeys at the Scopes trial in Tennessee.

III. The 27th of August, 1859, marked the world's first successful drilling of an oil well, in Titusville, Pa. Only six days before the announcement of Darwin's theory, the oil age began. From this almost unnoticed grease spot arose literally the Wright brothers, Henry Ford, the superhighway and super traffic jam, more deaths than have come from all our wars, the multiplication and corruption of travel, smog, traffic ulcers, safety belts, and the totem-pole leer and grimace of the crazy, mixed-up 1959 cars.

IV. Karl Marx published *Zur Kritik der politischen Ökonomie,* the forerunner of *Das Kapital,* spawned in the quiet of London's vast libraries. The seeds of communism were sown. The whirlwinds are still being reaped.

Today, a hundred years later, history has yet to say whether efforts to achieve real human liberties, or the theory of evolution, or the technical repercussions of the age of oil, or the incubus of Marx will lay the most fateful hand upon us.

But medicine was stirring. In 1859 our parent organization, the American Medical Association, was a lusty adolescent of twelve years. Its journal, a faint glint in the editorial eye, was a dream to be realized twenty-six years in the future. Elizabeth Blackwell, the first woman physician of modern times, having been graduated from Geneva College ten years before, was entered on the British Medical Register, marking the penetration of woman into another hitherto exclusively masculine domain. This was but part of the larger struggle against all manner of disenfranchisements where color, sex, creed, or greed had disbarred all save a small entrenched minority. In 1859, the earliest chair of medicine in the Americas, established at Salamanca, was two hundred eighty-one years old. In England the Royal Society of London was sedately marking its two-hundredth year. Only five years had past since the posthumous publication of Daniel Drake's epochal work, *The Diseases of the Interior Valley of North America,* the first real comprehension of medical ecology since Hippocrates' *On Airs, Waters, and Places.* Theobald Smith was born, Northwestern University Medical School opened, and the Transylvania Medical School closed its doors. The demonstration of the effectiveness of anesthesia and its rapid acceptance had opened new vistas for surgery fast being glutted by a hideous harvest of infection, iatrogenic but not recognized as such. The brilliant demonstrations by Holmes and Semmelweis of the contagiousness of puerperal fever were hooted down by the sophistry of the pompous professors and carriage-trade practitioners, another sorry example of the ignorant bilking the innocent. Although it was just fifty years since a backwoods surgeon, McDowell, had dared to defy tradition and do what was just not done, ovariectomy was still hardly respectable.

Man's inhumanity to man was observed in shocking display at the battle of Solferino in north Italy where on the 24th of June, 1859, the Franco-Sardinians under Napoleon III unexpectedly met the Austrian army under Francis Joseph. There were disastrous casualties. Thirty-nine thousand soldiers were left dead, wounded, and unattended when the survivors fled in the field in all directions. The next morning Henri Dunant, a Swiss, did the best he could as a one-man rescue team. From that day on he tried to improve the lot of the wounded soldier. His efforts culminated in the founding of the International Red Cross which has had as its mission the relief of those caught in disasters of all kinds and in particular during periods of war an effort to fulfill any possible mission of humanity. Thus from an unlikely start 100 years ago some good arose out of much evil.

In 1859, Florence Nightingale published her *Notes on Nursing,* and the next year was to establish at St. Thomas' Hospital the first modern school for the training of nurses. More recently the emphasis on a *trained nurse* far too often has been on training and not nursing. Virchow's *Cellular Pathology* was a year old, as was Gray's *Anatomy* for which an unkind reviewer predicted an early and painless death. Landry described a form of acute ascending paralysis still known by his name. Physiology was advancing. Pfluger published his monograph on electrotonus. This same year he succeeded Helmholtz as Professor of Physiology at Bonn. Graefe described retinal embolism only eight years after Helmholtz had invented a practicable ophthalmoscope. Bundsen and Kirchoff dis-

covered spectrum analysis. The monk Gregor Mendel was working busily on his sweet peas which were to reveal basic laws of genetics and heredity.

American medicine was still in bondage to Europe, save in the hands of a few exceptional persons. One truly great American physician, Daniel Drake, was already being covered with the unmerited ashes of oblivion. Physiology and chemistry were emerging in Germany, which was soon to take the lead in clinical medicine from England whence it had come from Paris and Dublin.

"Wonderful little, when all is said,
Wonderful little our Fathers knew
Half their remedies cured you dead,
Most of their teaching was quite untrue."—*Rudyard Kipling.*

We can survey the next hundred years briefly by using life expectancy at birth as a measure of adding to life chronological years, however tawdry and drab they may be in an age which bows in reverence before the often empty maw of television but has little respect for its elders.

The Past Hundred Years: I. First Decade, 1859-1869

A man born here a hundred years ago had a life expectancy of about forty years, twice that of a Roman citizen at the height of the empire. Internal medicine was not a specialty. We began hand in hand with man midwives, in the Section on Practical Medicine and Obstetrics. The first crisis was the Civil War, for which neither side was prepared, medically, militarily, or morally. The medical lessons were mostly negative. Disease killed many more than shot or shell. Military medicine in the first war fought with railroads as supply lines and the telegraph for communication relearned Napoleon's bitter lessons of staff work, supply, evacuation of wounded, and the savage surgery which often compounded the injury of those broken by the weapons of the day. But diseases of filth and hunger preyed on soldiers in camp as well as captives in the cruel prisons of war. The Surgeon General's medical treatises about the war of rebellion were gruesome catalogues of the fruits of man's inhumanity to man, scarcely tempered by the awkward and small medical help of the day. There was little by-product of medical gain from all the blood, infection, and suffering.

II. Second Decade, 1870-1879

A man born ninety years ago had a life expectancy of about forty-one years if we can trust the somewhat uncertain statistics of the day. The A.M.A., representing the doctors of the country, made the first real efforts to heal the wounds of civil war. Several presidents of the A.M.A. were former Confederate medical officers. Meetings were held in Southern cities. Thus physicians, looking at their fellow man without rancor, helped ease the afterpains of internecine war, an example unheeded by their rabid political brethren. Medical education was still in the hands of the incompetent, guaranteeing that the dictatorship of the dull would continue. Cholera and yellow fever came in perennial epidemic waves along the seaboard and up the navigable rivers. The names of pest houses, homes for incurables, and lunatic asylums disclosed society's reactions to its sick.

In 1873 the obstetricians decided to stand alone. Our section lost them, but we took on others and became the Section of Practical Medicine, Materia Medica, and Physiology. This was an early hint of the close association of internal medicine and basic science.

Internists as such had not appeared, but physicians skilled in diagnosis and therapy were gaining recognition, status, and sometimes affluence. In the eighties two societies of internists were begun. In 1884, the American Climatological Association was started. Since then it has shifted its emphasis with the years. Now it is the American Clinical and Climatological Association, as tuberculosis has lost some of its lethal sting. In 1886, the Association of American Phy-

sicians was established. These two organizations have had a strong influence on American medicine, a steadying conservatism more than progressive innovation.

III. Third Decade, 1880-1889

A man born eighty years ago looked forward to living forty-two years. Little had been added in twenty years. In Europe, Pasteur and Koch were establishing the basis for the germ theory of disease, which was resisted with pontifical dogmatism here and abroad, not least by internists. The university system of medical education in Germany was bearing fruit in the dazzling advances in the use of chemistry, physiology, and pathology to promote a more nearly rational medicine. In America, where cults have had a high birth rate and not entirely high enough death rate, there was much hue and cry. Antivivisection was the special preoccupation of meat-eating, fur-bearing spinsters whose specious and vicarious love of animals did not cover up the fact that they despised their fellowman. Antivaccination zealots exemplified once more the power of ignorance over innocence. The efforts of Jefferson, Franklin, and Waterhouse were not thrown out, since the slow self-correcting mechanisms which society uses to right itself when unbalanced were wisely and strongly urged by physicians in this and other sections of the A.M.A.

IV. Fourth Decade, 1890-1899

The average person born seventy years ago, and many of you happily are with us today, could look forward to a life expectancy of forty-five years. If you had been average you should have been dead these twenty-five years. Thus, the growing understanding of infections, hygiene, and preventive medicine began to stretch out the life span to the point where many can die now without any assistance from germs. For American medicine the most significant event was the opening of the Johns Hopkins Medical School. The wise benefactions of a wealthy Baltimore merchant left a fortune in the trusteeship of farsighted men who were not snarled in the red tape of any codicils which claimed to forsee the unforseeable. For the first time in America the medical school was part of a university. The students were scholars, the equal of any graduate student, and women gained equal access. Secondly, the hospital, though separate, was *under the control* of the medical school. Thus it was possible to combine a hospital's primary mission of mercy with the not less important missions of teaching medicine and advancing medicine by research. Clinical study began to get equal status with preclinical research and helped in the judicious fusion of these separate elements of medical arts and science to benefit the patient. Four of the eight early leaders of medicine at Johns Hopkins came from Michigan where medical students had worked in laboratories for a long time in contrast to the didactic or strictly clinical methods of Yale and Harvard. Mall, Abel, Howell, and Hurd thus brought the impact of Midwestern state schools, stemming directly from the Jeffersonian tradition, to the wise men of the East. This vital influence has been forgotten in the obvious and important contributions from German universities.

To digress for a moment—whence came the influence which advanced science in Midwestern schools when classical and humanistic studies dominated the theological cast of New England universities? Probably the origin can be traced back as far as the Ordinance of 1787, establishing the Northwest Territory from which the states of Indiana, Illinois, Michigan, Wisconsin, and part of Minnesota were subsequently derived. This was the first territory in which the Federal Government prohibited slavery forever. The law required that a certain porportion of the land be set aside to support public education. When Michigan was admitted as a state, in 1837, every 16th section of land was set by for education. From each section 3,000 acres were designated for the support of the University of

Michigan. The administration of funds was in the charge of a Superintendent of Public Instruction. Thus some of the flagrant exploitations which pock-marked the early history of other states did not exist. Furthermore, the Board of Regents which launched the University of Michigan had two first-class scientists, Henry R. Schoolcraft, the great explorer and naturalist steeped in Indian lore, and his colleague and companion, Dr. Zina Pitcher. Stephen T. Mason was Governor of the Territory and the State of Michigan most of the time from 1831 to 1840. He had a vital part in the foundation and inauguration of the University. Mason, a Virginian, was steeped in knowledge of the scientific activities and ideals of Thomas Jefferson. The program used in the establishment of the University of Michigan followed so closely Jefferson's course established at the University of Virginia that a coincidence is improbable. The claim that the University of Michigan was planned along the lines of the Prussian system of education is invalid. When Thomas Jefferson wrote out his plan for the organization and development of the University of Virginia, in 1812, Prussia had no system of education. Furthermore, at the University of Michigan, even in the early 1840's, German was not taught at all, whereas French, Italian, and Spanish were. As a final evidence of Michigan's respect for science when the New England schools were heavy in theology is the fact that the original Board of Regents got $10,000 appropriated for the purchase of scientific apparatus and books when the budget of Harvard University for such things was nil.

Osler's contribution to internal medicine in America is the most far-reaching of all that we can recognize. His textbook was the internist's Bible for half a century. The influence of pathology, the avoidance of useless therapy, and the rich contributions of natural history to biology became established. As a humanist, teacher, and physician, Osler taught American doctors that scholarship was respectable and compatible with superb competence in the practice of medicine. By inadvertance Osler played another important role in internal medicine in America. This came from the impact of his textbook, with its frank admission of therapeutic vacuum, in leading to the establishment of the Rockefeller Foundation and the Rockefeller Institute. The many far-sighted persons who directed the affairs of these and similar organizations made possible the development of full-time clinical teaching in this country. Osler's genuine opposition he would surely change today. From such beginnings internal medicine has developed.

Growing pains of this section and a certain ambivalence about our name appear. In 1890, we became the Section of Practical Medicine and Physiology. In 1891, Physiology was dropped. In 1892, it was the Section of the Practice of Medicine. You see that uncertainty about the mission of internal medicine is not new.

Across the Atlantic new forces were at work. Asepsis was growing out of Lister's antisepsis. The x-ray, discovered by Roentgen in 1895, was to bring the internal parts of the body into view in a way which made possible many of the later developments of internal medicine. At home Theobald Smith, born, you remember, in 1859, discovered the tick as vector in Texas cattle fever. Preventive medicine was to make other advances, reaching their acme in Walter Reed's experimental demonstration of the mosquito's role as a carrier of the invisible germ of yellow fever. But perhaps most important of all, Pierre Curie, in work which was the culmination of the efforts of many physicists and chemists, discovered spontaneous radioactivity. A new force was aboard throughout the lands of the world, for good or evil.

V. Fifth Decade, 1900-1909

The average life expectancy of a man born at the turn of the century was forty-eight years. In a period of fifty years science had added almost a decade to the span of years a newborn babe could expect

to live. Though homeopathy was fading out, as cults do whenever the corporate wisdom of a community reaches a certain level, osteopathy and chiropractic, systems of putative cure built on illusion, were lurking to take up the ancient mulcting of the optimistic ignorant. They remain a tribute to ignorance. Their survival bears a reciprocal relation to community intelligence. Whenever they have reached legitimate objectives it has been through use of the science and arts of regular scientific medicine, not diagnostic "machines."

Deficiency disease, the notion that positive harm, lesions, and death can be caused by a minus sign, a lack, demonstrated that nature does indeed abhor a vacuum. How long the obvious causes of malnutrition, and recognized cures had to wait for solution is illustrated in vitamin C and Lind's forty-year wait for the Lords of the British Admiralty to heed his demonstration. But the chemists waited over one hundred years more before they got at the fairly simple chemistry of ascorbic acid. The first group of graduates of full-time medical schools were spreading new ideas in medical teaching in some of the more alert schools.

Other forces were coming into focus in internal medicine. The earliest journal devoted to this field, the ARCHIVES OF INTERNAL MEDICINE, was born in 1908. The name Archives, mellifluous and august, had no connection with the missions of the journal. Inner medicine was a direct borrowing from German internists who did not want to get themselves confused with or contaminated by the skin men. For the first time in the United States, clinical investigators in many different fields had a place to publish their exciting but often neglected research. In this decade the American Society for Clinical Investigation, frustrated by the dilatory pontifications of the senior Association of American Physicians, split off as the Young Turks. This warning was so little heeded that two generations later another group, denied a place at the table of the elect, seceded and is thriving in competition with the no longer very young Turks.

VI. Sixth Decade, 1910-1919

Who can encompass and digest the vast revolution of the last fifty years in American medicine? To be sure, one born fifty years ago could look to fifty-two years on the average before the grim reaper would mow him down. Twelve years added in sixty years seems too good to be true, as every medical orator on every occasion said in one way or another fifty years ago. But in this country in 1910 the education of doctors was still a scandal, the outcry muted only because there was still too little that doctors could do. The great turning point in our century of internal medicine came in an accomplishment so utterly unexpected that we have not yet comprehended either its method or its results. Internal medicine, being a part of medicine which requires and depends upon study, discipline, and thinking, has profited in untold ways from this event in our history. A scholarly and perceptive layman gained easy entrée into all American medical schools to study them as institutions of learning. His welcome everywhere was warm, probably because they all expected their obvious needs to be eased by a grant from the Carnegie Foundation. What Abraham Flexner, son of an immigant peddler, found and shouted from the housetop was a scandal of such vast proportions that to read his report today is to see dark ages, with medical education in the hands of minor-league robber barons. Recently I read Flexner's report of the shabby wretchedness of medical education. There was hardly a medical school in the modern sense. There were no internists anywhere supported as scholars, caring for the sick, teaching, and investigating. Internal medicine or clinical medicine could not exist until there was a hard core of dedicated teachers, doctors, thinkers who could be free from the thralldom of practice but responsible for a few patients so that their teaching did not mistake poison ivy for ivory tower.

The teens were relatively sterile of great advances in medicine though there was much activity pointing to the next break-through. World War I gave physicians guilty feelings of satisfaction. Now for the first time doctors were smart enough to keep the well from dying of bacteria, while the designers of destruction proved that steel is stronger than muscle and blood and poison gas than the lining of the lungs.

Still, in this decade in the Western world for the first time in the course of man's history and earlier, a *Patient* going to a *Doctor* had better odds than 50-50 of profiting by his visit. While history has always known great and just cures, the *vis medicatrix naturae* rarely got her share of credit for healing the many who were not too impatient or important to bide their time.

Soon after the start of World War I Osler wrote a paper entitled *The Coming of Age of Internal Medicine in America* (1915). The rise of teaching hospitals and medical clinics worthy of the name was continuing. There was much heat about full-time clinical teaching which Osler, exemplifying, opposed. Subsequent events have verified the point that excellent clinical teaching does not flourish without scholars devoting their time, their talents, and their lives wholeheartedly to this most difficult cluster of pedagogic tasks, the teaching and training of physicians, the care and cure of the sick, and the advancement of learning by research.

VII. Seventh Decade, 1920-1929

The infant born early in this decade could look to a life expectancy of fifty-six years. Here we taste the first fruits of clinical investigation, taking the problems of the wards to the laboratory and returning to the bedside to test the results. Banting and Best cracked wide open the problem of diabetes with the isolation of insulin. Minot, Murphy, and Whipple combined sound basic research with clinical wisdom to provide clues to the cause and management of pernicious anemia which are still solving some of the mysteries of metabolic mechanisms. In 1924, the launching of the *Journal of Clinical Investigation* provided a new outlet for the work coming from the growing laboratories. In 1925, Flexner's second report detailed the really extensive advances which private wealth, used as a wise catalyst which gained state and other support, had been able to accomplish in establishing full-time clinical teaching as a going concern despite vigorous opposition and honest misgivings. The age of specifics was about to dawn.

VIII. Eighth Decade, 1930-1939

A major depression, a slowing birth rate, and the recurrent naive notion that panacea was at hand could not obscure the fact that a child born in America had a life expectancy of sixty-three years. Sixty-three, the grand climacteric of the Romans, the three-times-three-times-seven, was now the legitimate hope of a whole nation. In eighty years science had made a present of twenty-three years of life to each child born in the United States. Wards and hospitals here and there over the country were now the scene of basic clinical studies which showed the limitations of natural history alone in curing the sick. Internal medicine was growing on a sound base which even the invention of a nonofficial Board for Certification of Specialists cannot thwart, though because of it the training of internists has tended to become rigid and inflexible. Sulfonamides, the first real victory in the therapy of infections, gained a Nobel Prize for Domagk which he could not take because Hitler had succeeded, without too much protest from physicians, in stultifying German medicine which was reduced to a paltry craft in the hands of dealers in duplicity.

IX. Ninth Decade, 1940-1949

The small citizen born in 1940, given some luck with traffic and atomic holocaust, was scheduled to live for sixty-six years,

more than a quarter of a century longer than his great-grandfather could expect. In medicine the massed phalanx of students of infectious disease was ready to spring to attention if another pandemic of influenza burst forth. They also served who only stood and waited, for hepatitis was the major infection in World War II, surprising the experts as much as did the mushroom-shaped cloud which might blow us all away. From the pain, the agony, and the suffering a few advances came. Well-adjusted but thoughtful extroverts like Winston Churchill could still arouse a nation eased by luxury so that they defeated a paranoid maniac who had the ear and eye of his mechanically duped people. The Germans lost a war, the Russians gained time for development, and American physicians and scientists had a chance to look around.

Medicine suffered an almost fatal setback when Nazi doctors used Jews and other expendables for their foolish experiments, conniving in mass murder and mass torture. American doctors witnessed mass slaughter with atomic power. Forces still only vaguely understood were unleashed against a civilian population, a throwback to the terrible destruction of whole societies by Attila the Hun. Antibiotics came close to answering Ehrlich's prayer with the mass production of penicillin and its ever-increasing tribe of relatives in broad and narrow spectra of therapy. Meager gain for the destruction of many tens of millions of persons came in the careful study of man in his machines of death—planes, submarines, ships, tanks, or alone in foxhole or on patrol in enemy territory. Fierce extremes of cold and heat and how best to get men into and out of them were studied. Space, gravity, loneliness were all being faced as part of the lot of mechanical man as he survived almost totally destructive war. But above and beyond all this was the demon—man's latest opening of Pandora's box, the atom bomb—fission, fusion, finale? Internal medicine sharing guilt and ignorance with all others, showed no signs of having raised up a new man, wise, and loving enough to decide man was worthy of fighting larger enemies, or whether he should be left to exploit his talents in destroying himself.

X. Tenth Decade, 1950-1959

These last ten years, cold war, beatniks, the easy buck, the pathetic search for security in a world from which security has vanished—these days we know too well. Internal medicine has come of age, but only as part of a much larger whole of scientific medicine. An infant born in this decade may now hope to outstrip the Biblical three-score years and ten, since, barring atomic or automobile destruction, his life expectancy at birth is seventy-three years. Governmental support of research has brought forth a new army of investigators, partly at the expense of reduced teaching. Medical education itself is now the subject of experiment, though so far none is designed to give clear answers. Labor now bids fair to outstrip capital in a contest designed for the benefit of a few at the top of the managerial revolution. A hundred years ago, let the worker beware. Then the employee became responsible for gross negligence. Soon a worker in trouble without overt injury successfully blamed his employer and was compensated. Next they say disease comes from work or is made worse by work. Finally all sickness becomes the fault of the employer. Fringe benefits rise, leisure and long life are at hand, but for spectators seeking a modicum of security to be spent in boredom. Sickness insurance, beginning mostly as a system of paying surgeons for piece work, has not yet found a way of having the patient share in cost. Always let someone else take the responsibility. The complexity of all the new diagnostic tests, therapeutic procedures, and drugs has increased the cost of being sick. Hospital costs have soared with contracting work week, raised labor costs, and unending increase in the complexity of the work a hospital does. Antiflouridation propaganda

reveals man's eternal talent for paranoid self-bewilderment. These are but a few waves of the vast new sea of problems for the future.

So much then for a glimpse of the first one hundred years of the Section of Internal Medicine. One result of such forces is a new kind of doctor—the internist. But what is an internist?

We have chosen or inherited a poor name for our specialty. The bemused layman often does not know an internist from an intern. The name inner medicine began in Germany when dermatology budded off and it was feared that there might be some cross contamination between mother and child. Even the simplest soul knows what a surgeon is. Obstetricians, having outgrown their midwifely origins, are understood. But what is an internist and what is internal medicine? I remember my confusion before I began to study medicine, when a second year medical student told me that his most interesting course was internal medicine, which I thought was the entire program. But internal medicine has been defined by exclusion as what was left over when all the other specialties had been subtracted. Definition by exclusion is no better than diagnosis by exclusion.

Internal medicine differs from general surgery in having retained most of its component parts. Ophthalmology, otolaryngology, urology, neurosurgery, gynecology, orthopedics, and plastic surgery have splintered off from general surgery. Proctology and thoracic surgery seek the heady air of independence. Though in some schools medicine has lost dermatology and neurology with great harm to all, it still keeps as lusty siblings in the family, cardiology, metabolism, infectious diseases, geriatrics, endocrinology, allergy, pulmonary diseases, oncology, hematology, nutrition, and others. As I have said, "where they are taught and practiced best cardiology, allergy, endocrinology, neurology, hematology and nutrition are wings of a single mansion and not outhouses."

Internal medicine may be defined as the principles and practice of the arts and science of medicine which depend upon the careful evaluation and care of the adult patient in the light of his ecology; his history, signs, and symptoms; his structure and his function as influenced by his environment. It is not committed to a method of examination or technique of treatment. It enlists the aid of specialists in any field for assistance. Internal medicine can contribute most for the patient where it is learned by hard study and discipline and taught by scholars who have mastered the skills of teaching, the crafts of the clinical arts, and the accuracy of laboratory science in the care of the patient. Such is the lesson of the first hundred years of our Section. Guard it well. For if our student companions do not excel and exceed us, the future will be no better than the present, and the passage of time will make no marks on the calendar of progress for the next celebration of a centennial of this Section.

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Discussion of Direct Relief of Coronary Occlusion

The Anatomic Pathologic Problem

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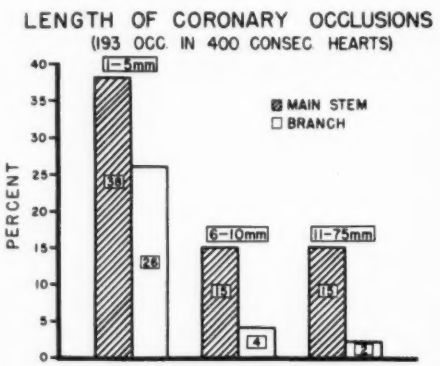
The Central Problem

The therapeutic problem in coronary artery disease is created by the existence of structural coronary narrowing or complete occlusion causing diminished coronary blood flow. The reestablishment of a satisfactory blood supply then becomes the central objective.

The Nature of the Occlusion

Excluding the more unusual causes, such as embolism, syphilitic narrowing of the coronary ostia, necrotizing arteritis, or calcific aortic stenosis impinging on the ostia, one deals with coronary atherosclerosis as the causative process in more than 90% of patients with angina pectoris or acute myocardial infarction. An effective therapeutic approach must be based on knowledge of the anatomic changes and of the pathologic physiology of the atherosclerotic process.

The Anatomic Characteristics of Coronary Atherosclerosis.—The obstructing atherosclerotic lesions are arterial, not venous, and reside in the main stems and primary branches. They are almost entirely epicardial. The highest incidence of occlusions is not directly at the mouth of the vessel but a short distance distal to the mouth.[1] Over half are within 3 cm., and 70% are within 4 cm. of the coronary ostia. The lesions are mostly localized and segmental and consequently make surgical correction feasible. In a study of almost 200 occlusions of the main coronary arteries and their branches in a series of 400 hearts, 64% were less than 5 mm. in length, 40% were less than 3 mm. in length.[1] More than one-half of all the occlusions were in the main stems, the remainder in the main branches (Figure 1). Approximately one-third of the main stem occlusions were 6 to 75 mm. in length and might pose considerable technical difficulty if endarterectomy were attempted. In some instances, fibrosis and calcification may involve not only the intima but also the entire media. In 100 consecutive hearts with occlusions regardless of clinical diagnosis, there were 248 occlusions, or an



Percentage of total number of main stem and branch occlusions related to the length of the occlusions.[1]

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average of 2.5 occlusions per heart. Only 33 of these hearts had only one occlusion. Atherosclerotic narrowing or occlusion of a coronary artery may be caused by an atheroma with progressive fibrosis, by a superimposed thrombus, by intramural hemorrhage in an atheroma, or by rupture of an atheromatous abscess. Thus, in 6,800 consecutive autopsies, thrombosis on an arteriosclerotic basis (43%), arteriosclerosis with or without infarction (41%), and intramural hemorrhage (8%), presumably on an arteriosclerotic basis, made up 92% of the causes of occlusion, with the remaining 8% distributed among embolism, inflammation, and syphilis.[2] Thrombosis usually develops at a point of stenosis produced by an arteriosclerotic plaque where the intima is roughened or broken.

Any surgical approach also must recognize that the structure of the epicardial and myocardial arteries may be markedly altered even in the absence of atherosclerosis.[3,4] The arteries are metabolically active structures and participate as do other tissues in the aging process. The media, initially made up of circular smooth muscle and elastic fibers, and the adventitia, a meshwork of connective tissue containing elastic fibers, both lose their elastic fibers with age. These changes are most rapid in the left anterior descending artery and slowest in the right coronary artery. The myocardial arteries undergo fibroelastic changes in the intima and media and atrophy of the smooth muscle in the media and develop irregular patches of connective tissue. These changes may pose technical difficulties in endartectomy or similar procedures.

The Effect of Acute Coronary Occlusion

When a coronary artery is suddenly and completely occluded in a previously normal heart, a myocardial infarct is usually produced. This sequence is observed experimentally and clinically. The coronary arteries consequently must be considered to be end-arteries in the physiologic sense.[5] The size of the infarct, however, is always less than the total territory supplied by the artery.[6] This is related to the fact that minute intercoronary capillary and other fine connections less than 40μ are normally present. These may be readily demonstrated in the normal heart by injection of a colored watery solution into a coronary artery and observing its immediate appearance in all other areas of the heart supplied by the other coronary arteries. The peripheral border of the infarcted muscle may be supplied by blood oozing through these fine channels or, as Wiggers[7] maintained, by diffusion from the surrounding myocardium.

Within a minute after acute occlusion, myocardial contraction diminishes progressively as ischemia continues. As the contractions become feeble, they are balanced by the intraventricular pressure, and the ischemic area expands paradoxically with each systole.[5] The small collateral channels that normally exist in the coronary arterial system do not supply enough blood to support useful contractions for many minutes.

In an extensive study of 1,200 human hearts, the clinical manifestations were interpreted on the basis of the findings disclosed by the Schlesinger technique.[8] By this technique, the coronary arterial system is injected with a lead-agar suspension which penetrates regularly as far as 40μ in diameter. Only the larger intercoronary communications that have been demonstrated to be functionally important are delineated by this method.

In hearts of 9% of normal men, larger intercoronary communications, 40μ or larger, may be observed.[8,9] They are not sufficiently numerous to prevent infarction, however. Clinical, electrocardiographic, and pathologic data indicate that the heart may recover without structural damage if the duration and degree of ischemia are not too great. Experimentally, myocardial ischemia produced by temporary occlusion of the main stem of a coronary artery for 40 minutes generally produces areas of ir-

reversible damage and necrosis.[10] At any time during or after occlusion, the heart may go into ventricular fibrillation or exhibit other arrhythmias. This may well be related to differences in the gradient of oxygen tension.[11] To be effective, surgical removal of acute sudden occlusion would have to be performed within one half-hour, particularly since atherosclerotic involvement of other areas in the coronary system might be present. During the next few hours, one may anticipate, however, that some injured myocardial tissue might be redeemed and further extension of a thrombus might be averted.

The Effect of Gradual Coronary Occlusion

In human hearts with old occlusions, intercoronary collateral channels of a size greater than 40μ were observed in practically 100% of cases. These collateral vessels served as a by-pass or detour and supplied the myocardium distal to the area of marked narrowing or occlusion from neighboring unoccluded arteries. This anastomotic circulation evidently develops as a compensatory phenomenon in relation to marked arterial narrowing or occlusion.

These phenomena have been reproduced by us under controlled experimental conditions in the domestic pig, the coronary arterial tree of which is strikingly similar to that of man.[15,16] Intercoronary collaterals of more than 40μ may be seen within 24 hours after marked coronary narrowing, but their rich development usually requires 7 to 21 days. After 5 to 12 days of preliminary narrowing, sudden acute occlusion of the narrowed artery no longer regularly results in death. Examination of the myocardium grossly and microscopically showed that these collaterals not only permitted survival of the animal but at times protected the myocardium from serious damage. Somewhat similar results in dogs have been reported by others.[17,18] Under favorable conditions the major portion of the coronary artery system can be gradually occluded with minimal or no infarction in the animals that survive.[17-19]

An indication of intercoronary collateral development also can be demonstrated experimentally by measurement of retrograde flow and pressure from a severed main coronary branch. Immediately after abrupt occlusion of a main coronary branch, the retrograde coronary flow approximates 5 to 5.8 ml. per minute compared with control values of 2 to 3 ml. per minute and is relatively constant in any one dog for a few hours.[20-22] Measurements of retrograde flow during temporary clamping of the other coronary arteries indicate that the latter are the major source of flow.

After long-continued obstruction of a coronary artery or a branch in an otherwise normal animal heart, the flow of blood from the cannulated end of the artery becomes very large. It begins to increase within a few hours, may double within two days, and become three to four times the control level within a week. Within a few weeks, the flows approximate the values for the normal rate of inflow before occlusion in that coronary artery or branch. The observation that the retrograde blood had the same content of oxygen and carbon dioxide as that in a systemic artery leaves no room for doubt that the collateral circulation is on the arterial side of the coronary capillary bed. The gradual augmentation of retrograde flow is attended by similar elevations of systolic and diastolic pressures in the peripheral end of the occluded coronary artery.

Observations of the heart post mortem in man are in accordance with these experimental studies and explain the apparent inconsistency between the presence of long-standing, obstructive lesions, on the one hand, and the absence or relatively slight pathologic or clinical evidence of myocardial damage, on the other hand. Indeed, the hearts of patients with angina pectoris may show one or more occlusions in two or even three main stems, a rich collateral development, and only scattered myocardial

fibrosis.[12] While there is a general relationship between the incidence of coronary occlusion and the occurrence of angina pectoris, other modifying factors, such as the exact site of the occlusion, the importance of the vessel involved, the adequacy of the collateral circulation, the rate at which such occlusions or narrowings develop, and the temporary influence of emotion and of vasomotor reflexes, are also of great importance. Although damage to the heart is minimized by the development of the collateral circulation, the margin of safety, or as it may be termed, "the coronary reserve," is reduced.

It is apparent from the foregoing considerations that either a palliative or a more basic approach to the problem of coronary heart disease may be considered. Palliative procedures include reduction of myocardial requirements by producing hypothyroidism with radioactive iodine[23,24] and interruption of pain pathways by sympathectomy and other denervation operations.[25]

Augmentation of Coronary Blood Flow by Nonsurgical Measures

Augmentation of the coronary collateral circulation beyond that occurring naturally after marked coronary narrowing or complete obstruction inevitably is limited because the extent of the natural development appears to be well nigh maximal and localized in the area where it is most effective. Vasodilator drugs have not been demonstrated to augment the rate of development or extent of intercoronary anastomoses.[16] In grossly normal hearts from anemic patients the incidence of anastomoses was 39% compared with 9% in grossly normal hearts from nonanemic patients.[9,26] Anemia may conceivably have some therapeutic application in the treatment of coronary artery disease, but to date its practical value has not been demonstrated.

Effect of Exercise on Augmentation of Blood Supply to Ischemic Areas

Augmentation of the coronary collateral circulation after a program of exercise has been observed experimentally by Eckstein after coronary occlusion in the dog.[27] Although the clinical implications are important, they do not afford a therapeutic approach of major proportions. Furthermore, exercise in dogs with coronary artery occlusions was attended by increased risk of myocardial damage and death.[27] It is a plausible assumption that anoxia is the factor that stimulates the formation of the collateral circulation after coronary obstruction, in anemia, exercise, cardiac hypertrophy, and cor pulmonale.[9,16]

Surgically Produced Increased Coronary Blood Flow from Extracardiac Sources

To afford direct relief by introducing a new source of arterial blood supply to the ischemic myocardium the following measures have been employed: application of grafts of neighboring tissues (pectoral muscle, omentum, lung, jejunum), production of pericardial adhesions, myocardial insertion of an actively bleeding artery, anastomosis of the coronary venous system with neighboring arteries, and ligation of internal mammary arteries.[28-34] Many of these procedures have been undertaken in the hope of effecting a more even distribution as well as an increased supply of oxygenated blood.

Partial Ligation of Great Coronary Vein or of Coronary Sinus.—This has been done to induce passive venous congestion of the myocardium and dilatation of all the minute vessels. This has been combined by Beck[31] with anastomosis of an artery to the coronary sinus. The necessity of two operations in the latter procedures, an operative mortality of approximately 15%, degenerative changes in the veins, and evidence that the heart is not permanently benefited have limited the acceptance of this procedure. Narrowing of the coronary sinus by itself, with or without narrowing or ligation of other veins, likewise has not proved generally successful. The remaining veins dilate and minimize the initial effect.

Promoting Extra Cardiac Blood Supply by Pericardial Adhesions.—This has re-

ceived more widespread acceptance. Limited evidence of increased blood supply is available. Plachta, Thompson, and Speer[35] demonstrated enlarged extracardiac arterial communications at autopsy in treated human clinical cases. Experimentally, continuity of arterial channels between the heart and the extracardiac tissues through the adherent connective tissue scar has been demonstrated by the injection of India ink or similar fine materials. Channels of capillary size suffice to convey India ink. Convincing evidence of a significant increment of coronary blood flow by such procedures has not been presented in all the years that this approach has been studied. That some patients experience clinical improvement in angina pectoris after cardiopericardiopexy seems definite. The fact that this improvement occurs immediately after operation suggests that interruption of afferent sensory pathways may be the mechanism that is operative. That suggestion may also be a factor is indicated by patients' reports of improvement after sham mammary artery ligations.

Direct Implantation of Artery into Myocardium of Left Ventricle.—Implantation of the upper bleeding end of the left internal mammary artery into the muscle mass of the left ventricle has been proposed and extensively studied by Vineberg and his associates.[32] His observation that the implanted open end can form anastomoses with terminal branches of the coronaries has been confirmed by others.[36] Unfortunately, intimal hyperplasia, medial thickening, and ultimate luminal obliteration usually ensue, but, according to Bailey, progressive narrowing in other main coronary vessels may prevent these occlusive changes. The magnitude of the additional blood supply and the distribution of this accessory supply in patients after operation cannot be stated.

Coronary Artery Surgery: The Direct Attack

Coronary Artery Resection with Vascular Graft Replacement.—As in peripheral artery disease, the employment of autogenous vascular grafts and artificial prostheses has been attempted in coronary artery disease. To date, the occurrence of thrombosis and occlusion in animals has discouraged application of these techniques to patients.

Interarterial Anastomosis.—The side-to-side or end-to-side anastomosis of a patent vessel with the neighboring patent segment of a coronary artery distal to the point of occlusion could provide important relief to an ischemic area. The identification of the patent artery and of the site of the occlusion in the atherosclerotic artery, the absence of pathology in the segment distal to the occlusion, and a favorable anatomical relationship between the two vascular channels to be joined would be among the elements necessary for the success of the procedure.

Endarterectomy

Coronary Endarterectomy.—This attack aims directly to eliminate pathological narrowing or occlusion and restore vascular patency.[37,38] Practically all patients with angina pectoris have had severe narrowing or complete occlusion of at least one main stem. Even in hearts with two or more occlusions, the removal of one or several areas of occlusion may be expected to result in improvement. This improvement might result from restoration of patency throughout the entire vessel or from an improved source of collateral circulation within the area of the operated-on or neighboring vessels consequent to the removal of one or more of the occlusions. The fact that the occlusions occur almost always near the ostia and are in the superficial vessels accessible to attack greatly favor this procedure. Moreover, the patency of the smaller coronary vessels within the myocardium favors maximal myocardial nutrition with whatever blood is made available.

On the other hand, the usefulness of endarterectomy is somewhat limited by the longer length of occlusion witnessed in one-third of human hearts and by the occasional vessel with the entire wall completely fi-

brosed and calcified. In some hearts with many occlusions, the usefulness of this method would be expected to be somewhat diminished. It is pertinent in this connection to recall that in 108 hearts of patients with angina pectoris due to atherosclerosis, 312 old healed coronary occlusions were found at postmortem examination. Significant clinical improvement even in such advanced patients is not impossible, however. This frequency of multiple narrowings and occlusions, the problem of postoperative thrombosis and occlusion of the injured vessel, and the need for accurate preoperative determination of the location, number, and extent of the lesions are some of the problems attendant to this approach. The recent advances in techniques of coronary angiography have led to some progress in the preoperative localization of these obstructions. Because of its demonstrated risk, radiographic and surgical experimentation in patients with normal hearts is reprehensible and not to be condoned.

Summary

Surgical methods to increase effective coronary blood flow to the heart by bringing to the heart an additional blood flow by anastomoses with various adjoining tissues or by the implantation of a systemic artery to the myocardium have been limited by the anatomical lesions and the consequent functional changes in the coronary arterial system. It is not always realized, moreover, that capillary intercoronary anastomoses exist normally and not infrequently extend from the heart via the pericardial reflections to neighboring structures such as the aorta or pulmonary artery. These communications can be readily demonstrated by the injection of watery solutions into a coronary artery, after which the injected solution becomes immediately discernible elsewhere over the heart. These fine connections are of no immediate functional significance, for they do not protect the myocardium from infarction if a coronary artery is suddenly occluded. Accordingly, demonstration after operations of such fine communications between the heart and surrounding structures by colored water solutions or India ink is of little clinical importance. To demonstrate functional collateral channels, either extracardiac or interarterial coronary anastomoses, more viscous injection masses which require larger channels should be used and the size of the vessels which such injection materials delineate should be determined.

Nor are there any convincing blood-flow studies to date which demonstrate that any therapeutic surgical operation leads to a sustained increase in arterial blood flow in a heart with prior coronary narrowings or occlusions. Caution must be observed in applying the results of experiments on the normal dog heart to the diseased atherosclerotic human heart with its established narrowings, occlusions, and rich network of compensating intercoronary anastomoses.

The clinical evaluation of operative procedures designed to increase the myocardial blood supply is also beset with difficulties. The nerve pathways from the heart to the nerve roots are not clearly defined. They traverse a wide pathway and may be interrupted by the operative procedure. Further studies are needed to evaluate this possible factor. Whether the survivors will have an augmented life span or a reduction in the number and size of infarcts will be almost impossible to determine because of the inherent unpredictability of the clinical course. Previous studies have shown that the mortality rate in patients with angina pectoris in the first year after onset is high and is less thereafter when the disease has become more stable.[39] This knowledge of the natural history of angina pectoris indicates that the therapeutic results in a group of such patients may be affected by the stage of the disease at the time they undergo treatment as much as by the therapy itself.

The surgical procedures that have been attended with success in the treatment of peripheral arterial disease, namely, endarterectomy, bypass, patching, and anastomo-

sis are now being applied to the treatment of coronary artery disease. Taking into account the anatomical and pathologic physiological changes incident to atherosclerosis of the coronary arteries, one may anticipate gratifying results if suitable patients can be accurately selected by radiography without undue hazard and if the technical difficulties of the appropriate surgical procedures can be surmounted.

Conclusions

1. The following anatomic and pathologic features are favorable to a direct surgical approach for coronary artery disease.

a. At least 90% of all instances of acute myocardial infarction and angina pectoris are due to coronary atherosclerosis.

b. The lesions are localized and segmental; approximately 60% are less than 5 mm. in length, and 70% are within 4 cm. of the coronary ostia.

c. The lesions are epicardial and therefore surgically accessible.

d. More than one-half are in the main stems; the remainder are in the main branches.

e. The patency of the smaller coronary vessels within the myocardium favors maximal myocardial nutrition with whatever blood is made available to them.

2. The following features of coronary atherosclerotic heart disease may pose difficulties.

a. Approximately one-third of the main stem occlusions are 6 to 75 mm. in length and may prove troublesome if endarterectomy is attempted.

b. In some instances, fibrosis and calcification may involve not only the intima but the entire media.

c. Multiple occlusions are frequently present in patients with angina pectoris; removal of one or more of the occlusions may, however, improve myocardial blood supply by restoration of patency throughout the entire vessel or improve the source of collateral circulation.

d. Surgical manipulation of the relatively small coronary arteries and branches, the problem of possible postoperative thrombosis and occlusion of the injured vessel, and the need for accurate preoperative determination of the location, number, and extent of the lesions are some additional problems attendant to a surgical approach.

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Diagnostic and Functional Evaluation of Candidates for Coronary Endarterectomy

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The development of a new operation for the treatment of a serious disease must progress through a number of preliminary stages, involving animal and cadaver investigation, before it may be offered to the diseased human being. When the operation is finally ready for trial in the diseased patient, particularly if it carries an expected high risk, it must be offered at first only to patients so desperately ill that they are willing to accept any risk for the sake of possible benefit. Above all, the diagnosis in these patients must be beyond doubt.

In the case of coronary endarterectomy as devised by Longmire, Cannon, and Kattus,[1] the chief medical problem was to establish the diagnosis of coronary occlusive disease beyond doubt. Of secondary importance was the problem of obtaining some form of quantitative or at least quasi-quantitative evaluation of the patients which might provide a baseline from which postoperative results could be measured.

To date, 11 patients suffering from incapacitating angina pectoris have been subjected to direct-vision coronary endarterectomy. There have been six fatalities and five survivors. In the fatal cases, the coronary arteries were carefully dissected at autopsy and the areas of occlusion and marked narrowing were noted. In the survivors, the coronary arteries were carefully palpated at the time of operation. Areas of complete occlusion were detected by palpation of the firm rigid areas of artery surrounded by densely adherent fat. Confirmation of the occlusion was obtained by clamping the suspected area and watching the ECG for at least six minutes. If *T*-wave or *ST*-segment changes occurred, it was concluded that the vessel was carrying blood; if no ECG alteration occurred, it was taken as evidence that the vessel was completely occluded and endarterectomy was undertaken at that site. Complete occlusion at the site was proven in each case by removal of the occluding plug at operation or by postmortem dissection. In some of the survivors, the status of the left circumflex artery could not be determined with certainty because of inaccessibility of portions of this vessel from the approach permitted by the surgical exposure. Thus, the diagnostic methods employed in the study of these patients could be assessed in light of the anatomical distribution of the coronary occlusive disease.

Case Selection

In the selection of patients for this new surgical procedure certain preliminary criteria were adopted. Since the operative risk was expected to be high, it was decided that only patients who were totally incapacitated and incapable of carrying out their regular employment would be considered as surgical candidates. Furthermore, it was decided that operation would be undertaken only on candidates who wanted the operation after having all risks made known to them. Any doubt about the diagnosis would exclude the patient from consideration.

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On the basis of these criteria, twenty-three patients who had been referred or had presented themselves for consideration of surgery were evaluated. Fourteen of this group were considered suitable candidates for coronary endarterectomy. Eleven have had the operation. Of the three who were not operated on, one 40-year-old man died suddenly before he could be scheduled for surgery; one patient has been deferred because of extensive atheromatous disease of the lower extremities with claudication; the third has been deferred for administrative reasons.

Eight patients have been rejected as candidates for operation. Five of these had confirmed diagnoses of coronary insufficiency. Reasons for not recommending surgery were as follows: Three were men who were able to continue their usual occupations as waiter, chiropodist, and fish butcher with use of nitroglycerin when necessary. One was a 67-year-old woman with familial hyperlipemia. It was felt that she was a poor surgical risk because of her age and furthermore dietary control of the hyperlipemia offered a chance of affording relief of her symptoms. The other patient was a 65-year-old semiretired physician who wanted the operation but was still able to carry on limited consultation practice. He subsequently survived a posterior myocardial infarction. In two patients the diagnosis of coronary insufficiency could not be substantiated by exercise tests even though the histories were reasonably convincing for angina pectoris. One 54-year-old woman complained bitterly and excessively of pain which seemed atypical and closely related to emotional upsets. Because left bundle branch block precluded electrocardiographic confirmation of coronary insufficiency, operation was not recommended.

Establishing the Diagnosis

In the cases submitted to operation our primary concern was to be certain of the diagnosis of angina pectoris due to coronary atherosclerosis. The classic clinical-pathologic correlations of Blumgart, Schlessinger, and Davis [2] assured us that if the diagnosis were correct, at least one of the three main coronary branches (right, left, anterior descending, or left circumflex) would be completely occluded. The presumption was that the occluded vessel could be worked on without compromising the remaining circulation to the myocardium.

In the Blumgart correlations, the diagnosis of angina was based primarily on the history and no electrocardiographic data were employed. The original observation by Feil and Siegel [3] of transient electrocardiographic *ST*-segment depression during anginal pain which could be reproduced by exercise has laid the groundwork for the objective ECG tests of coronary insufficiency, as exemplified by Master's test,[4] the anoxemia test of Levy,[5] and the exercise stress tests of Scherf.[6]

In establishing the diagnosis, we have insisted that the history be highly suggestive, but the electrocardiogram must disclose nonfixed *ST*-segment depression either at rest or after exercise. The *ST*-segment shift need not be accompanied by pain.

In all but one of our patients operated on, these conditions were met unequivocally. Four of the cases had resting ECG's within normal limits, and two had *Q*-waves in Leads III and *AVF* suggesting old posterior infarction. All of these six had positive Master's two-step tests. One case had such severe leg claudication that he could not perform the Master's test. In this man, *ST*-segment depression was produced by having him lift weights with both arms for less than one minute. In three patients there was *ST*-depression at rest which could be observed at different times with or without pain. The ECG changes along with the typical histories in 10 of the 11 patients left no doubt as to the diagnosis of true angina pectoris. In one patient an atypical history and equivocal exercise

ECG test led us to employ coronary angiocardiography as a diagnostic method.

Description of Treadmill Test

Having established the diagnosis and then having made the decision to operate, we were faced with the problem of obtaining some sort of semiquantitative baseline from which to evaluate the postoperative results. A treadmill exercise test was therefore devised which was patterned after the one reported by Bruce, Yu, and their associates.[7,8]

A transthoracic electrocardiographic lead is strapped securely to the patient's chest with the left arm electrode at the V_4 position and the right arm electrode in the right posterior axillary line. The right leg electrode is also placed at another position on the chest for grounding purposes. The ECG machine is then run at the Lead I switch setting. After a suitable period of rest sitting, the patient ascends three steps to the level of the treadmill where he rests standing until the tracing stabilizes. In some patients, the three-step ascent was enough to produce changes in the tracing.

The patient then walks at a standard speed of 1.75 miles per hour with the treadmill tilted to a 10% upgrade. In some instances, the speed was reduced to 1.5 miles per hour; in other instances, particularly in postoperative patients, it was accelerated to 2 or 2.5 miles per hour. In some instances, the ECG was run continuously, but in others 10-second strips were run at intervals during the exercise. There were some cases in which the exercise tracing was distorted by gross fluctuations of the baseline due to muscular activity of the chest. This problem was eventually solved by having the patient step off the treadmill and hold his breath for three to five seconds while a stable tracing was recorded. Walking was promptly resumed. The time at which the first ECG changes appear is noted. The patient then reports the onset of anginal pain. He continues walking until the pain reaches the degree of intensity at which he would ordinarily take nitroglycerin. Exercise is terminated at this point, and the patient sits down. Tracings are continued until the pattern has returned to the preexercise control or until it ceases to change. The patient reports the time at which pain disappears.

Results of Treadmill Tests

Tests on two athletic young men, 28 and 30 years of age, disclosed that they were able to exercise almost to the point of exhaustion without *ST*-segment deviation. The results of one of the tests is shown in Figure 1. Ten patients with negative Master's tests who complained of vague chest pains were able to walk for periods of 10 to 20 minutes without deviation of the *ST*-segments. Two of these had valvular heart disease, with *T*-wave inversions in the resting tracings. Four or five surviving patients have been able to walk 15 to 20 minutes without altering *ST*-segments.

Figure 2 depicts a continuous tracing of a treadmill test on a 52-year-old Japanese-American fish butcher who had complained of intercapsular pain and a sense of constriction in the lower throat with exercise. The pain had not prevented him from carrying out his usual work. Relief could be obtained as quickly with rest as with nitroglycerin. He is one of those rejected for surgery. The tracing is reproduced in its entirety because it is the prototype of the typically positive test. *ST*-segment depression appeared in 20 seconds. Pain was first discerned at 1¾ minutes, but walking was continued an additional minute as the pain continued and the *ST*-segments became more depressed. After cessation of

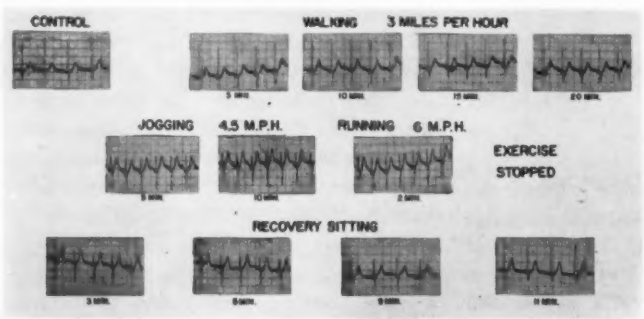


Fig. 1.—Treadmill test on a 28-year-old man in good physical condition exercised almost to the point of exhaustion. Despite changes in *QRS* and *T* amplitudes, no *ST* deviations are seen.

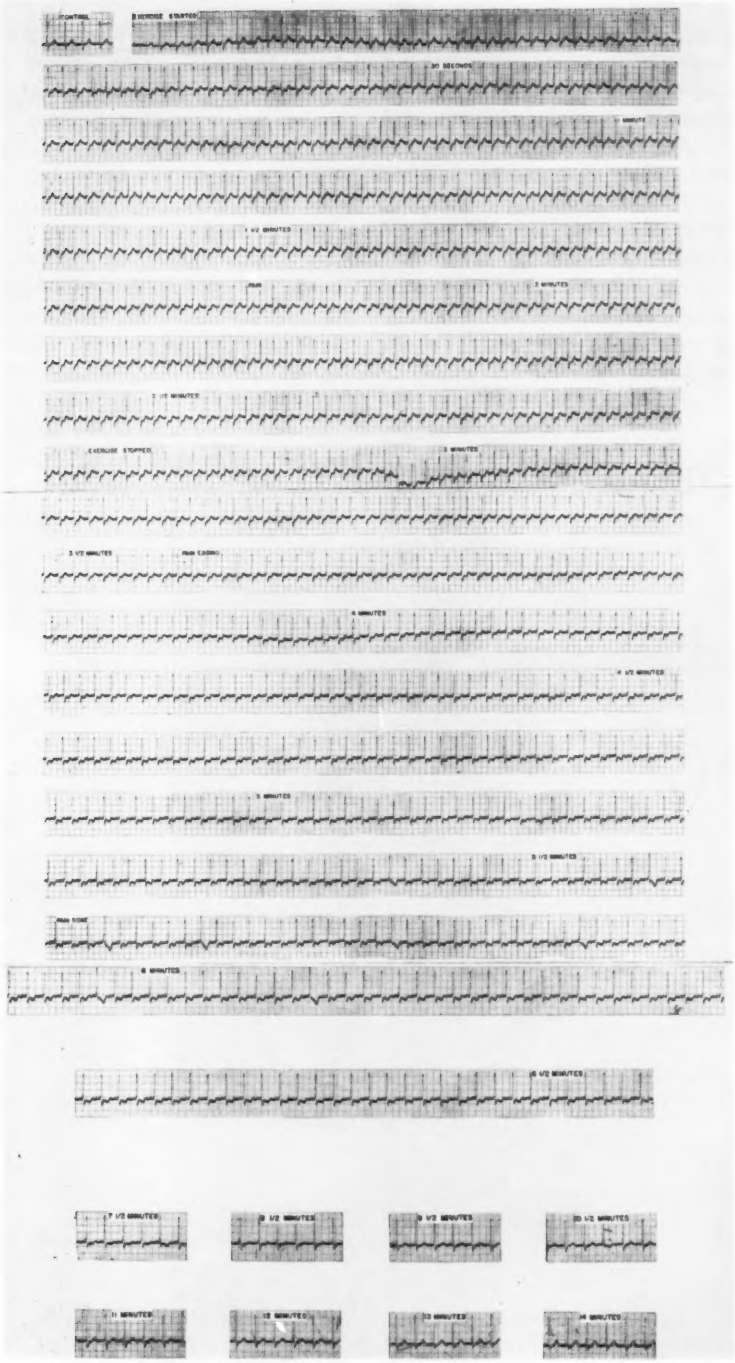


Fig. 2.—Continuous recording of treadmill test in a patient with mild angina pectoris which is not incapacitating.

exercise, the *ST*-junction gradually returned toward the isoelectric line, but the *ST*-segment began to tilt downward as the T-wave became lower. This change reached maximum development about three minutes after exercise at a time when the pain had disappeared. It is interesting to note that a number of Wolff-Parkinson-White complexes appeared at this stage. There was then a gradual return toward the control pattern which was reached about 11 minutes after cessation of exercise.

Four of eleven patients who were subjected to coronary endarterectomy had exercise tracings which conformed to the above description. One patient was not available for study, since his evaluation was carried out in another hospital. One patient had only mild changes, but it was possible to study him on only one occasion prior to surgery. Four patients had *ST*-segment depression in resting tracings. One patient showed an atypical response in which the chief alteration of the ECG tracing produced by exercise was the appearance of increasingly frequent ventricular premature beats progressing to bigeminal rhythm.

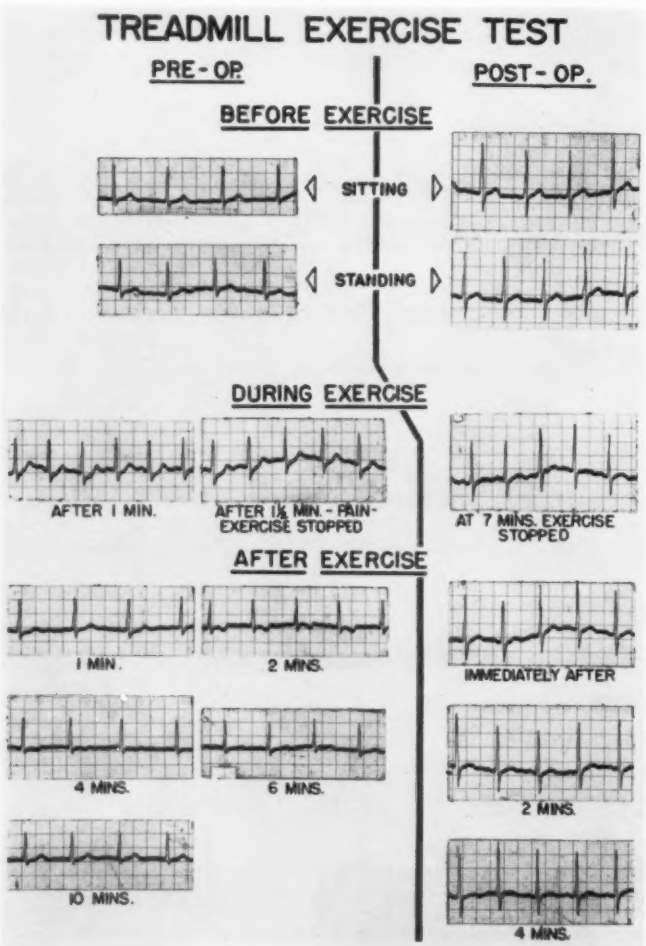


Fig. 3 (Case 1).—Treadmill tests before and after operation. Reproduced with permission from Longmire, W. P., Jr.; Cannon, J. A., and Kattus, A. A.: *New England Journal of Medicine* 259:993, 1958; The Massachusetts Medical Society, Boston.

Comparison of Pre- and Postoperative Treadmill Tests

Since the primary purpose of the study was to formulate a method for evaluating the results of surgery, it is of interest to compare pre- and postoperative treadmill tests on the four surviving patients available for study. Cases 1 and 4 are considered to be virtual cures, since both of these patients have been restored to full activity and are capable of heavy physical exertion. Their studies are illustrated in Figures 3 and 4, showing positive preoperative and negative postoperative studies. Subsequent studies up to one year after operation in each of these patients have disclosed no deviations of *ST*-segments in walks of up to 20 minutes duration at 2.5 miles per hour speed.

Case 3, illustrated in Figure 5, has postoperative anginal pain requiring nitroglycerin on rather strenuous effort. He has not been able to resume his usual work as a plasterer but has switched to sales work. While his postoperative tracings show some variations in the *T*-wave patterns, there are no changes in *ST*-segments and he has been able to walk up to 15 minutes on one occasion without pain.

Case 5 was the most severely disabled patient in the entire series. Frequent pains at rest would not respond to nitroglycerin and required meperidine (Demerol) for relief. The effort of turning over in bed usually produced anginal pain. There were frequent ECG tracings showing marked *ST*-depression at rest, although at times only the effect of digitalis could be dis-

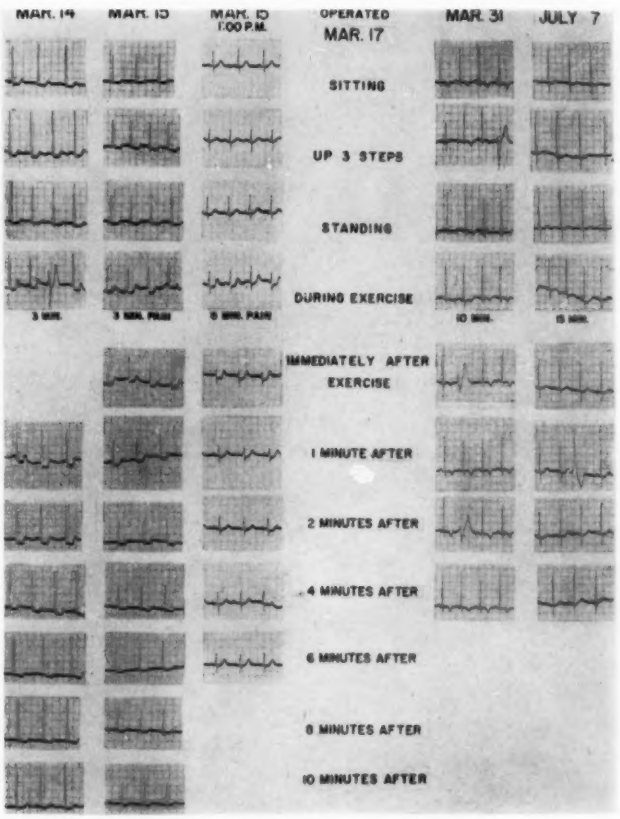


Fig. 4 (Case 4).—Treadmill tests before and after operation. Reproduced with permission from Cannon, J. A.; Longmire, W. P., and Kattus, A. A.: *Surgery* 46:197, 1959; The Society of University Surgeons.

cerned. One attempt at an exercise test resulted in such profound *ST*-depression on climbing three steps to the treadmill that it was quickly abandoned. Postoperative tests (Fig. 6) were mildly positive during the first two months, though on one occasion he was able to walk 10 minutes without pain.

On July 31, he returned to the hospital having suffered a major hemorrhage when a large abscess on his back was incised by a local physician without regard for the anticoagulant therapy on which the patient had been maintained. With the anemia (hematocrit 22) and the infection there was a return of severe anginal pain and of marked *ST*-depression in the resting ECG. He recovered satisfactorily and returned to his work as a salesman. Nine months after surgery, he was working full time. Exercise test at this time produced no *ST*-changes. The slight *ST*-junctional depression was thought to be due to digitalis (Fig. 7).

Patients with ST Depression at Rest

Among the fatal cases there were three patients who had *ST*-depression in the resting electrocardiograms. Case 9, who had frequent pain at rest, was not subjected to exercise. His tracings are illustrated in Figure 8. A tracing recorded during pain showed very marked *ST*-depression in the precordial leads. Nitroglycerin sufficient to abolish the pain brought about slight improvement in the *ST*-segments. On a subsequent day, there was *ST*-depression without pain. After 20 minutes of 100% oxygen breathing, the ECG pattern remained unchanged. After three days of

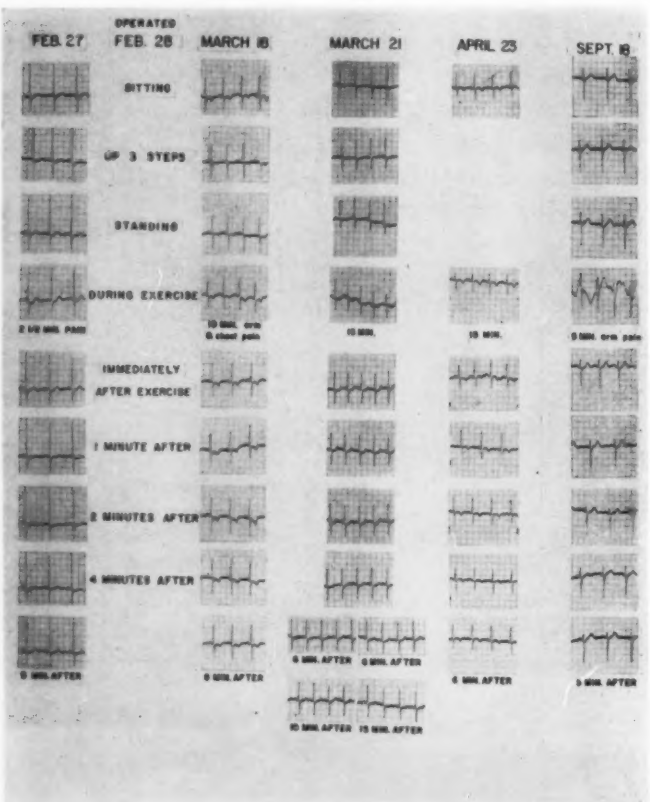


Fig. 5 (Case 3).—Treadmill tests before and after operation.

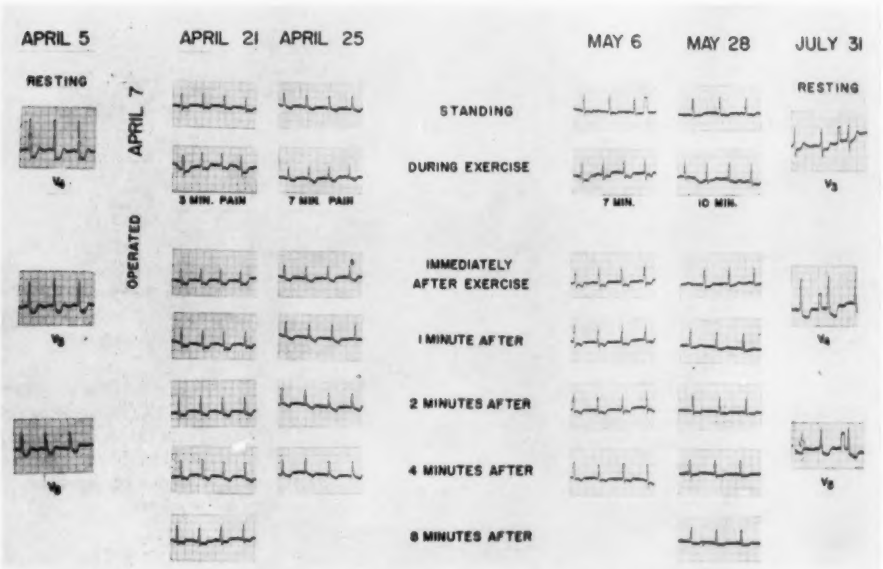


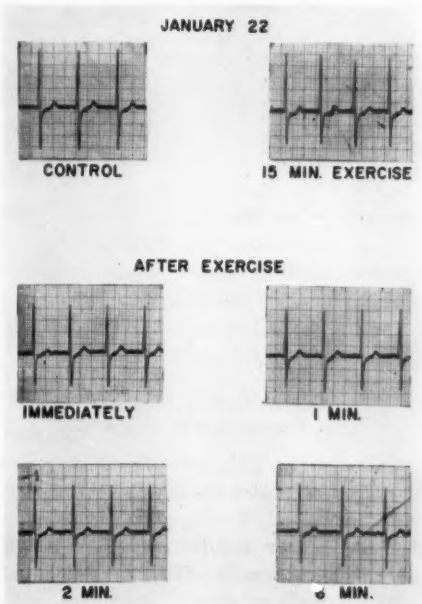
Fig. 6 (Case 5).—Resting tracings and treadmill tests before and after operation.

strict bed rest, there was improvement in the tracing but some *ST*-segment depression remained. Irreversible cardiac arrest occurred on the operating table. Autopsy disclosed microscopic areas of necrosis and fibrosis in the subendocardial portions of the left ventricular myocardium. There was complete occlusion of all three major coronary arteries, as shown in Figure 14.

Case 8 had *ST*-depression at rest but remained free of pain. Treadmill exercise resulted in the most marked *ST*-depression seen in the entire group of cases. This is illustrated in Figure 9. In the recovery period the tracing ultimately had less *ST*-depression than it had shown during the pre-exercise control period.

Case 7 (Fig. 10) was usually free of pain at rest despite persistent mild *ST*-depression. With exercise, there was prompt additional *ST*-depression and pain began in one minute. Nitroglycerin, 0.6 mg., was given during exercise, and pain abated as *ST*-segments appeared to improve. Within the next half minute, *ST*-segments again became depressed and pain returned. The

Fig. 7 (Case 5).—Follow-up treadmill test nine months after operation.



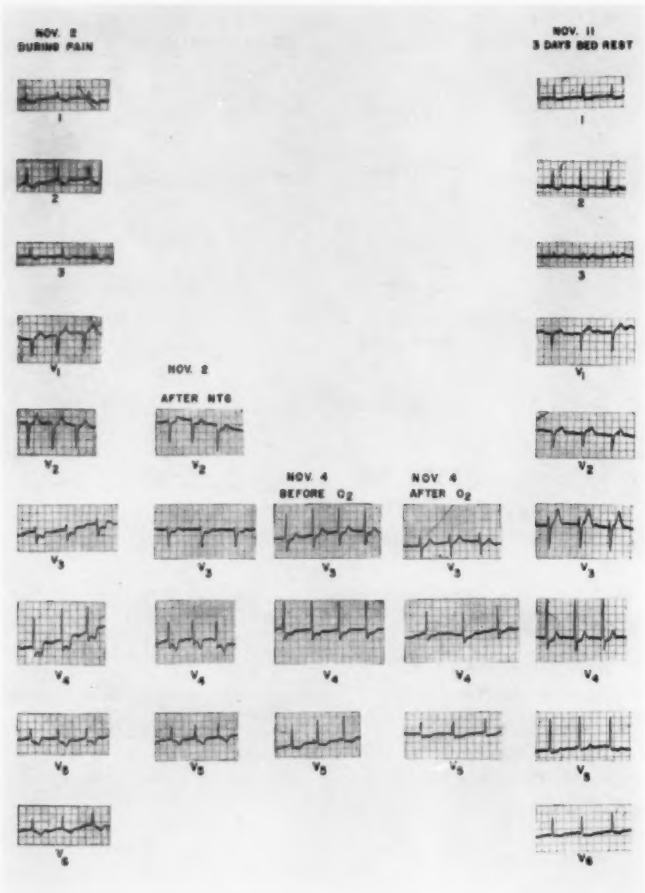


Fig. 8 (Case 9).—Resting ECG's showing effects of nitroglycerin, oxygen breathing, and bed-rest on depressed *ST* segments.

recovery period was characterized by deep *T*-wave inversions. On the next day, the test was repeated without administration of nitroglycerin. In this test, the changes were not quite so marked as in the previous one and recovery was slightly more rapid.

Cases Having Multiple Preoperative Tests

Case 2 (Fig. 11), who was free of pain at rest, was tested on three occasions before operation. The point of interest is that there were distinct variations in the patient's performance. He was able to walk longer periods of time on each successive test. The severity of the ECG changes, however, was maximal on the second test and minimal on the third test.

Case 11 provided the opportunity to carry out multiple treadmill tests prior to surgery. The effect of nitroglycerin and repetition of the test after a short rest were studied (Fig. 12). Comparing the tests of March 11 and March 20 reveals a similar response, although recovery was somewhat delayed on the second test despite the administration of nitroglycerin at the end of exercise. Nitroglycerin did not, therefore, have any influence in modifying the electrocardiographic recovery once the *ST*-displacement had occurred. After the tracing had returned to control levels and the pa-

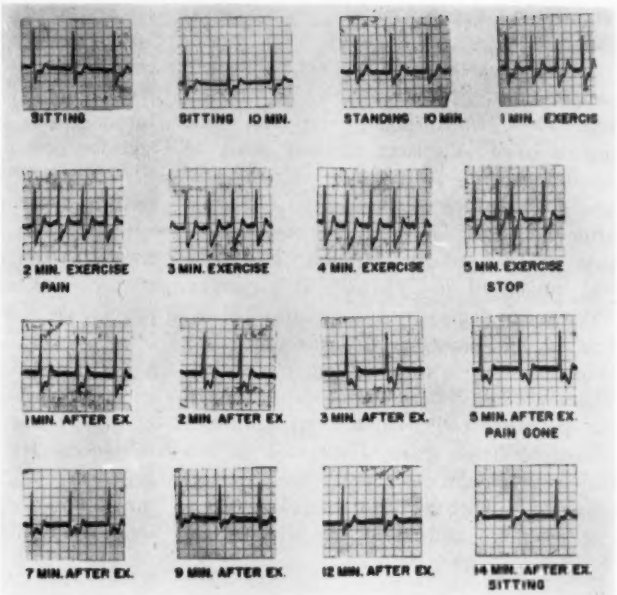


Fig. 9 (Case 8).—Effect of exercise on tracing which already shows *ST* depression at rest.

tient had rested for an additional five minutes, additional nitroglycerin (0.8 mg.) was given and the patient walked again. This time the onset of pain was delayed. It remained mild and never mounted to the intensity experienced in previous tests. Exercise was stopped at seven minutes because of fatigue rather than pain. Only the very

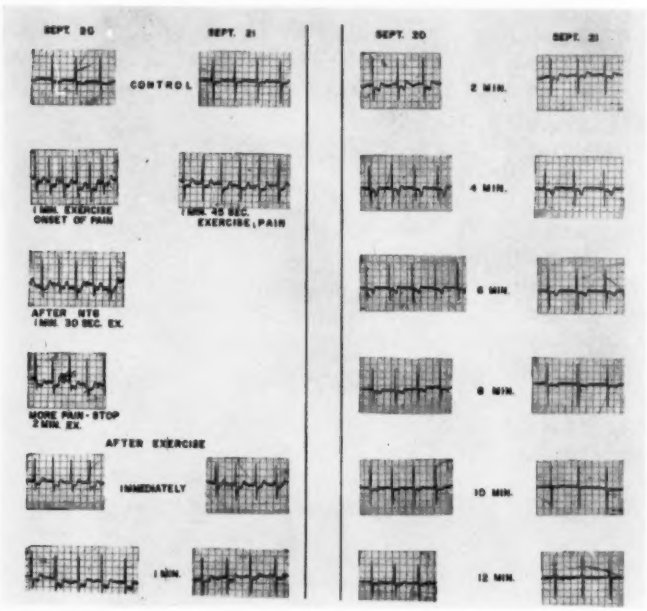


Fig. 10 (Case 7).—Treadmill tests repeated on each of successive days.

slightest *ST*-depression was discernible in the ECG.

Three days later, the patient performed two exercise tests separated by 30 minutes' rest. These two tracings produced the same degree of *ST*-displacement and pains of equal intensity. A day later nitroglycerin was given before the first exercise but not after the second. In both tests, the onset of pain was delayed and duration of exercise was prolonged to 3½ and 3¾ minutes. *ST*-segment depression was produced in the first of the two tests but was much less than that seen in runs without medication. There was no discernible *ST*-depression in the second test even though no additional nitroglycerin was given. The studies on this patient give clear evidence of the powerful effect of nitroglycerin in improving exercise tolerance and mitigating the electrocardiographic changes of subendocardial injury associated with exercise in the presence of severe coronary occlusive disease. At operation the completely occluded right coronary was endarterectomized. The left anterior descending was judged by palpation to have been occluded, and this was confirmed at autopsy four days later.

Case 10 was atypical in his response to treadmill exercise. Figure 13 depicts four tests carried out prior to surgery. In this patient, the chief ECG abnormality brought by the exercise was the development of multiple premature ventricular contractions. In the first test, on March 2, 1959, the onset of these preceded the onset of pain, but in subsequent tests the pain came before the premature beats. The patient, who was a careful observer, described increasing intensity of pain as the frequency of the

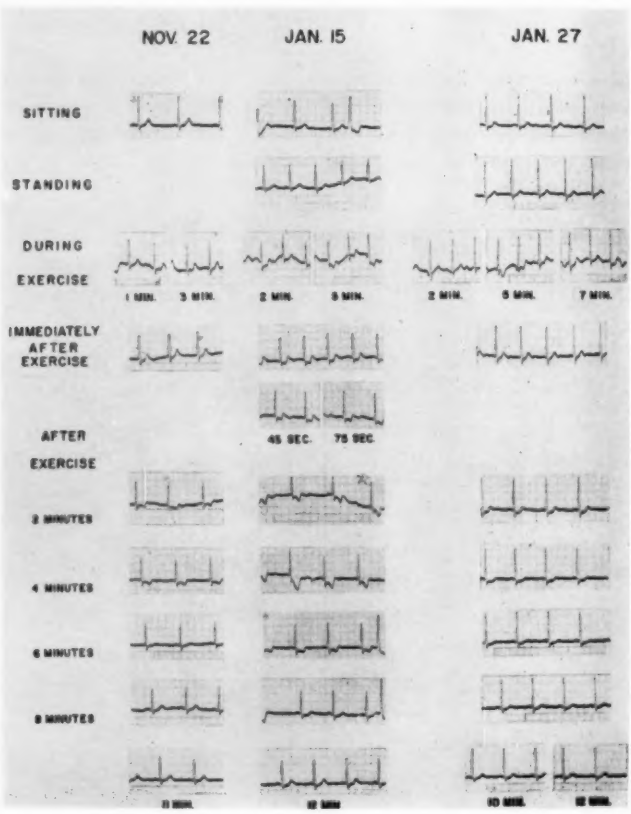


Fig. 11 (Case 2).—Repeated treadmill tests at fairly long intervals.

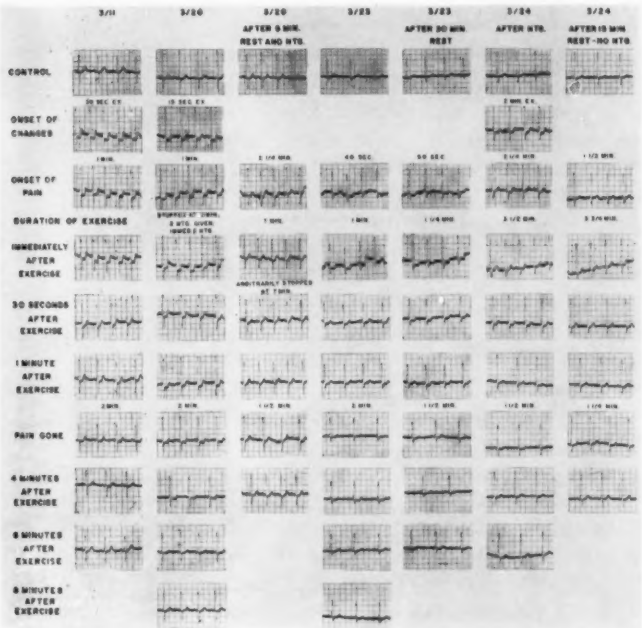


Fig. 12 (Case 11).—Repeated treadmill tests showing effect of nitroglycerin.

premature beats increased. Only slight *ST*-segment depression occurred, and this seemed to abate even during continued exercise. Exercise was terminated after eight minutes when the frequency of premature beats had reached 40%. Immediately after exercise there was sustained bigeminal rhythm with a 50% frequency of premature beats. *ST*-segments were isoelectric, although the T-waves which were previously inverted had become diphasic. All premature beats had disappeared two minutes after the end of exercise.

After ten minutes' rest, the test was repeated. This time, the performance was much improved. Pain appeared at four minutes of exercise instead of at two minutes as in the previous test. Premature beats were delayed in their onset and were much less frequent, reaching a maximum of 10%. The patient was able to walk for 10 minutes. *ST*-segment depression was not present in the immediate postexercise tracing and premature beats disappeared immediately after exercise.

During the next 24 hours, the patient was given 2 gm. of procaine amide, the last 0.5 gm. dose one hour before exercise. The performance under the influence of the drug was better than on the original test but not as good as on the second test of the previous day. He was able to walk 15 minutes, but premature beats had increased to bigeminal rhythm in the immediate postexercise period. *ST*-segment deviations were not observed. A subsequent test two days later resulted in definite 2 mm. *ST*-depression which could be observed during exercise but which disappeared immediately after stopping exercise. Premature contractions reached a frequency of 50% in the immediate postexercise period.

In this patient, the atypical ECG findings and his ability to walk for periods up to 15 minutes left some doubt that complete occlusion of at least one coronary artery could be assured. He was therefore subjected to coronary x-ray angiogram. A catheter was advanced from the femoral artery to the ascending aorta and 20 cc. of

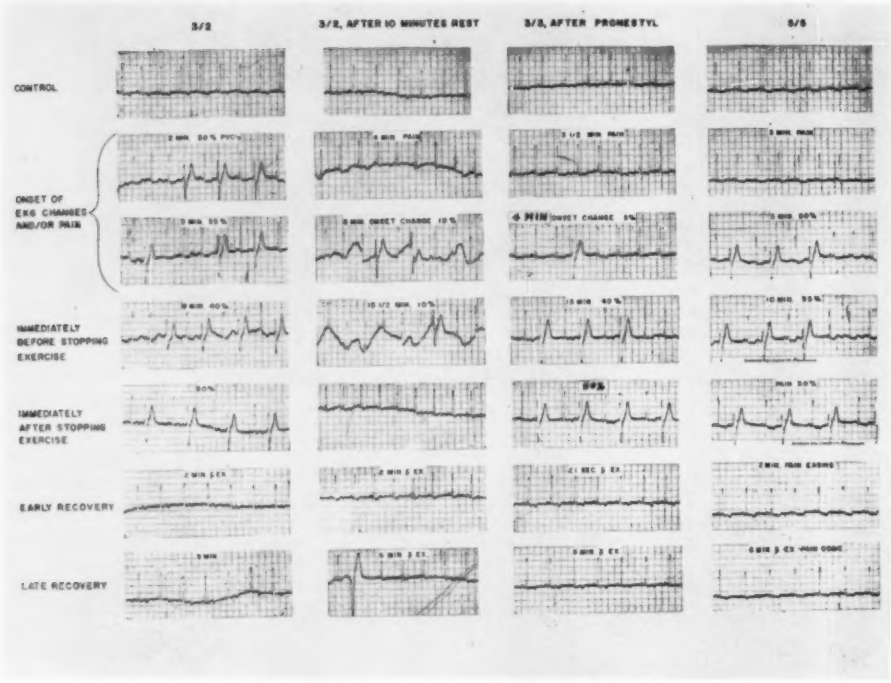


Fig. 13 (Case 12).—Repeated treadmill tests in which principal ECG change with exercise was onset of ventricular premature beats. Numbers given as percentages indicate frequency of premature beats.

diatrizoate sodium (Hypaque sodium) was injected under 5 kg. per square centimeter pressure. Using Elema biplane equipment, it was possible to obtain simultaneous right and left anterior oblique views with exposures at a rate of two per second. The right oblique disclosed a patent right coronary artery. On the left oblique the main left coronary could be visualized and a short portion of the circumflex could be seen. The anterior descending branch could not be seen except for a very short nubbin marking its origin. On the basis of the presumed total occlusion of the anterior descending branch and the urgent wish of the patient to have surgery, endarterectomy was undertaken. Irreversible cardiac arrest occurred on the operating table. The extent of the coronary occlusive process was much greater than suspected. As shown in Figure 14, there was an anomalous three-branched anterior descending artery, one branch of which was totally occluded over most of its length. The main left coronary artery was heavily diseased with only a pinhole opening leading into the circumflex which had a second area of occlusion about 2 cm. from its origin. The right coronary was patent proximally but was occluded in its distal portion at a terminal bifurcation.

Location of Occlusive Disease

Figure 14 illustrates the distribution of the coronary occlusive process in each of the first 10 cases, as determined either at operation or at autopsy. The invariable complete occlusion of the anterior descending branch is a striking feature of this series of cases.

All had evidence of additional severe disease in the right coronary, but in Cases 4 and 5 it was believed that occlusion was not complete in these vessels, since clamping

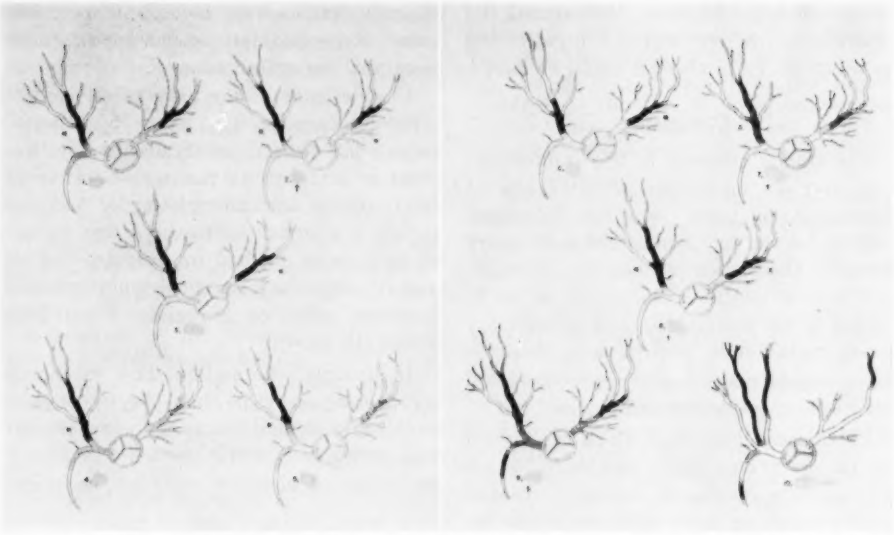


Fig. 14.—Diagrammatic representation of distribution of coronary disease in Cases 1 through 10. Solid areas indicate complete occlusion. Hatched areas indicate narrowing without occlusion. † indicates fatal cases; *, artery endarterectomized; *X*, artery endarterectomized in second operation; Δ, artery being worked on at time of cardiac arrest. Reproduced with permission from Cannon, J. A.; Longmire, W. P., and Kattus, A. A.: *Surgery* 46:197, 1959; The Society of University Surgeons.

them at operation resulted in prompt alterations of the ECG tracing.

Cases 5, 7, and 8, who had *ST*-depression at rest, did not appear to have more extensive disease than some others, who had normal resting ECG's. Case 9, however, who had continuous resting *ST*-depression, had complete occlusion of all three major coronary branches. His entire myocardial perfusion was flowing through a few small twigs branching from the large vessels proximal to the areas of occlusion. Case 10 was the only other patient who had complete occlusion of the circumflex branch. In this series, the left circumflex was the least affected branch.

It was not possible to make a correlation between the extent of the arterial disease and the variations of the electrocardiographic patterns in response to exercise.

Reproducibility

The various series of exercise tests which have been presented provide information on the reproducibility of the ECG changes associated with exercise in patients with severe angina. Case 7 (Fig. 10) had almost identical changes when tested on two successive days. Case 4 (Fig. 4) had less marked changes on the second of two tests performed on successive days. However, when the test was repeated on the second day, the patient was able to walk for a longer time, the *ST*-depressions were less marked, the *T*-wave changes did not occur, and the recovery was more rapid. This appeared to be a distinctly better performance than the previous one.

Case 2 (Fig. 11) showed an improved performance in the last of three tests performed at intervals of six weeks and two weeks.

Case 11 (Fig. 12) showed similar performances on March 11, 20, and 23. Case 10 (Fig. 13) showed an improved performance when testing was repeated after only a brief rest. After a few days another test showed distinct *ST*-segment changes which had not been observed before. This man showed improvement and then wors-

ening of his performance. In no case did repetition of the test lead to a negative test in which no ECG changes could be found.

Comment

The studies reported in this communication were not undertaken with the idea of developing a more sensitive diagnostic method for the detection of coronary artery disease. Their main purpose was to establish criteria which would enable us to be certain of the correct diagnosis of coronary artery occlusion in patients with incapacitating angina pectoris who were considered for coronary endarterectomy.

ST-segment depression which is nonfixed has proven to be a highly reliable indication of extensive occlusive coronary disease, usually involving more than one major arterial branch. In patients having normal resting ECG tracings, the positive Master's two-step test has been reliable in producing diagnostic *ST*-depression. In patients showing *ST*-segment depression at rest, it is not necessary to impose any further stress on the patient with the intention of reproducing the anginal pain; it has been shown by our studies, and by others long before us,[9] that in the progression of events leading up to anginal pain *ST*-segments become depressed before the onset of pain and often remain depressed long after the pain has disappeared.

We feel that *ST*-segment depression cannot be regarded as the only electrocardiographic evidence of occluded coronary arteries in the noninfarcted heart. This is shown by our case who reacted to stress by having multiple premature ventricular contractions rather than *ST*-segment deviation.

Whether or not the treadmill test will eventually prove to be a method for obtaining semiquantitative data on the severity of the coronary impairment cannot be ascertained from our experience. While two of our patients had highly reproducible responses to exercise, two others seemed to show improving performances and one showed deterioration in a later performance. Reproducibility would appear to be necessary for quantitation.

Despite some of the uncertainties of the treadmill exercise test, it has been useful in showing rather dramatically the improvement in performance that may be achieved by restoring flow through totally occluded coronary arteries. Moreover, it has proven to be a useful method for studying the effect of drugs on the anginal syndrome. The beneficial effect of nitroglycerin has been strikingly shown.

In patients who fail to show diagnostic *ST*-depression or in whom the response to exercise is atypical, x-ray coronary angiography may be a useful method for disclosing areas of complete coronary occlusion.

Summary

Twenty-three patients who were being considered for coronary endarterectomy have been evaluated from the point of view of establishing the diagnosis of coronary occlusive disease and of determining its severity.

ST-segment depression in the electrocardiogram has been associated with complete occlusion of at least one major coronary branch in 11 patients subjected to coronary endarterectomy. The *ST*-depression was present at rest in four of these, and in six it was induced by exercise.

Exercise on a motor-driven treadmill can be performed during continuous electrocardiographic monitoring. Patients with angina pectoris tested with this technique show ECG changes of varying degrees of severity which cannot be well correlated with the anatomic distribution of the coronary occlusive disease. Repeated treadmill testing may disclose improving performances in some cases and stable reproducible performances in others.

Treadmill testing has been useful in demonstrating objective indications of improved coronary perfusion in survivors of coronary endarterectomy. It has also been helpful in evaluating the effect of nitroglycerin

and procaine amide on the anginal syndrome. Coronary angiography may be useful in locating segments of coronary arterial occlusion.

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The Surgical Treatment of Angina Pectoris

WILLIAM P. LONGMIRE Jr., M.D.; JACK A. CANNON, M.D., and ALBERT A. KATTUS, M.D., Los Angeles

The studies of Blumgart, Schlesinger, and Zoll,[1] in reference to the role of coronary occlusion and the collateral circulation in angina pectoris, emphasized that the pain of angina pectoris is a manifestation of myocardial ischemia and that the underlying mechanism seems to be a relative disproportion between the demands of the heart for blood and the supply of blood through the coronary arteries. If the duration of ischemia, as in angina pectoris, is brief, no permanent myocardial damage may occur or only microscopic foci of necrosis and fibrosis may result. It was interesting that they found complete occlusion or narrowing of one or more major coronary arteries and their primary branches in the hearts of a considerable number of persons, which had not given rise to cardiovascular signs or symptoms. They state that complete occlusion of one or more major coronary arteries is compatible with comfort and longevity. Clinical signs and symptoms and the occurrence of myocardial damage depend upon whether the development of the intramyocardial collateral circulation has kept pace with the progressive arterial narrowing.

Every patient they studied, suffering primarily from angina pectoris without evidence of valvular disease or arterial hypertension, showed old complete occlusion of at least one major coronary artery. Twenty-three of twenty-nine patients, with or without valvular lesions and with angina pectoris as the primary symptom, showed complete old occlusion of two or more of the main coronary arteries. All three main coronary arteries were occluded in three of these patients.

All studies of this type[1-3] repeatedly stress the fact that occlusions occur in the major coronary arteries and their primary branches and that when they do occur myocardial circulation is maintained through the more distal patent branches and the anastomotic channels which develop between these distal branches. It may be inferred that the combined occlusion of major branches and distal arteries, which would thereby prohibit the development of a collateral circulation, would present a condition which would not supply an adequate circulation to support the heart beat. Szilagyi, McDonald, and France,[4] in an inquiry into the feasibility of applying direct surgical techniques to the correction of the occlusive process in coronary atherosclerosis, studied the distribution and state of advancement of the arteriosclerotic lesions in 190 hearts after injection of a barium-glycerin mixture at autopsy. They found evidence of the most advanced and widespread involvement in the hearts of those patients who had clinically suffered from angina pectoris. According to the criteria established by these authors, the rate of inoperability in the group of patients with clinical symptoms was 44%, the rate of possibility of palliation 43%, and the rate of curability 13%. They emphasized the desirability of an accurate method of determining the status of coronary circulation by means of angiography.

A number of investigators have studied the problem of coronary visualization by

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angiography. Cannon, Clifford, Diesh, and Barker,[5] in 1956, reported a technique of obtaining adequate coronary angiograms in dogs. However, a 35% mortality rate attended this procedure when performed on dogs which had previously survived ligation of a major coronary artery. These experiences naturally made us reluctant to employ coronary angiography in patients suspected of having coronary atherosclerosis. Thal and his associates,[6,7] as well as others,[8] have subsequently reported techniques that give roentgenographic visualization of the coronary arteries in humans with minimal risk. Our limited experience with these present techniques would indicate that caution must be used in the interpretation of such studies in regard to the location and extent of occlusive and stenotic lesions, although the need for an accurate preoperative evaluation of these lesions is great. Undoubtedly, further experience and improved techniques will increase the diagnostic accuracy of coronary angiography.

Current surgical attempts to improve myocardial circulations in cases of angina pectoris have been directed along two lines: (1) attempts to increase the intramural coronary anastomosis and thereby provide more efficient and effective utilization of arterial blood available to the heart and (2) increasing arterial flow both into the coronary arterial system and into available intramural collateral channels.

As indicated earlier, Blumgart et al.[1] have presented good evidence to support the view that anginal pain is related to myocardial anoxia and that such anoxia is produced when the delicate balance between the slowly advancing occlusive process and the development of collateral anastomotic channels is disturbed in favor of occlusion.

It might, therefore, be expected that procedures which improve intracoronary anastomoses would be of benefit up to the point where efficient blood distribution no longer remains a significant factor and total available coronary flow becomes the critical issue. The postmortem studies previously referred to[2-4] would suggest a surprising tolerance of the myocardium to a reduced total cross sectional area of the inflow vessels as long as intramural distribution is adequate. Brofman and Beck[15] state, "with progressive reduction of the lumen of a major coronary artery, coronary flow at rest is not compromised until the cross-sectional area approaches approximately 10% of normal." In the human, enough blood to support the heart beat can go through a stenosis of 1.5 mm. in diameter.[9]

The Beck I operation,[10,11] which consists of abrasion of the epicardium and lining of parietal pericardium, application of an inflammatory agent (0.2 gm. of powdered asbestos) to these surfaces, partial occlusion of the coronary sinus where it enters the right auricle, and grafting of parietal pericardium and mediastinal fat to the surface of the heart, has as its chief function stimulation of the development of intercoronary anastomosis. It is doubtful if any significant amount of extra cardiac blood is added to the coronary circulation by this procedure. In a series of 347 patients who had undergone this operation,[9] reported by Beck, 295 were alive at the time of the report, of which 278 were reported to have had a good or excellent result.

A similar procedure reported by Thompson and Plachta[12] was performed on 57 patients. Seven patients died in the hospital after operation. Of the remaining 50 patients, 90% were considered more than 50% improved and 40% more than 75% improved. The patients who died after leaving the hospital survived an average of five years, giving them an average lifespan of 9.5 years after the onset of the first symptoms. These authors concluded that the procedure was of definite value in palliation of symptoms and prolongation of life.

It has been demonstrated repeatedly that irritative substances placed within the

pericardial sac will increase the survival rates of dogs after ligation of the anterior descending coronary artery. It has been assumed that this increase in tolerance to coronary ligation is due to an increase in the intercoronary anastomosis. Gage, Olson, and Chardack,[13] using a method which produced delayed gradual occlusion of the circumflex and anterior descending branches of the left coronary artery, could demonstrate no beneficial effects of poudrage in terms of a decrease or delay in mortality nor a reduction in the incidence of gross infarction. These authors point out that the usefulness of any given indirect revascularization procedure will hinge upon its ability to provide an increase in collateral circulation above that produced by the disease itself.

The operation has the advantage of being relatively simple to perform, and, although in cases of angina decubitus a mortality rate of 39% has been reported by Beck, the operation has been attended by a low morbidity and mortality rate in the less severe cases. Despite the availability of this type of operation for over 20 years, it has never gained wide acceptance and has been enthusiastically supported by only a few surgeons.

Day and Lillehei[14] have recently introduced a new procedure designed to utilize the stimulation of hypoxia in the development of intercoronary anastomosis. The technique consists of constructing an amastomosis of measured size between the main pulmonary artery and the left atrium. The creation of this right-to-left shunt lowered the arterial saturation in dogs to 75% to 88%. Injection studies of the coronary arteries demonstrated that an increase in intercoronary anastomosis developed within one month after operation and that protection was afforded the heart of the dog when the coronary circulation was challenged by acute ligation of the circumflex coronary artery. Dramatic improvement was noted in one patient three months after this operation: the systemic arterial saturation ranged from 84% to 88%, but he was not visibly cyanotic. Calculations of blood flow through the shunt in animals appeared to be in the area of 20% of the total cardiac output. The tolerance of the heart with occlusion of one or more of the major coronary vessels to this increased cardiac output remains to be established. Blumgart, Schlesinger, and Zoll[1] found that associated valvular defects or hypertension, i.e., conditions which increased the myocardial work load, were associated with clinical symptoms in hearts with fewer major coronary occlusions than in hearts without this additional stress.

In an attempt to bring extra cardiac blood to the myocardium, Vineberg[16] proposed an operation which consists of freeing the internal mammary artery by ligating and dividing the intercostal branches from the fourth to the sixth interspaces. The artery is transected distal to the sixth interspace. The free end of the artery is pulled into a tunnel in the wall of the left ventricle. Before this is done, the sixth intercostal vessel is cut so that blood escapes from it freely into the ventricular myocardium. Pericardial fat-pad grafts are applied to areas of the myocardium which have been denuded of epicardium by sharp dissection. The results of this procedure in 59 patients were reported by Vineberg,[17] in 1958. Seventeen patients with preoperative angina decubitus had an operative mortality of 59%. By the term "angina decubitus" was meant simply the state of a patient who had anginal pain at rest without an exciting cause. Forty patients with no angina at rest preoperatively had an operative mortality of 5%, and 78% of the survivors were pain-free or had less pain postoperatively. Histological studies made on the mammary artery implant in patients dying postoperatively have shown open implanted vessels without significant intimal proliferation. Sabiston, Fauteux, and Blalock,[8] in experiments in dogs, noted that the subclavian artery, when implanted into the myocardium, usually remained patent, although only

small volumes of blood could be demonstrated to flow from the implant into the myocardium in the majority of preparations. Systemic arteries implanted into other structures, such as the liver, spleen, or sternomastoid muscle, became thrombosed regularly. Vineberg and others have been able to demonstrate that the transplanted vessel remains patent in a high percentage of cases and that anastomoses do develop with coronary vessels. Difficulties with thrombosis of the transplant and the adequacy of extracardiac blood added to the coronary circulation are the two uncertainties which have at present prevented wide acceptance of this procedure.

As another means of bringing additional blood into the coronary circulation in patients with angina pectoris, we have previously reported the technique of reestablishing blood flow through obstructed major coronary vessels by removal of the thickened atheromatous intima.[19] As pointed out, even in cases with extensive atheromatous occlusions these obstructions are apt to be confined to the main coronary arteries and their major branches. The major portion of the distal coronary tree must be patent for continual myocardial function.

After extensive studies on autopsy specimens and dissection of the coronary arteries of dogs, a suitable technique and special instruments were devised for this procedure in man by Dr. Jack A. Cannon.

Of the various types of clinical cases suffering from major coronary artery occlusion, it was felt that the most suitable group in which to apply this technique would be those patients with severe incapacitating angina without definite evidence of myocardial infarction. The studies leading to case selection for the operation have already been described by Dr. Albert A. Kattus.

Case Material

The heart has been exposed and the coronary arteries investigated in 10 patients with a diagnosis of severe incapacitating angina pectoris (Table 1). All of these patients were men, and their ages ranged from 38 to 63 years of age, with seven of them between 50 and 60 years old (Table 2). The clinical symptoms in all cases were very typical, with varying patterns of radiation of pain. Only 1 of the 10 patients did not have a history of pain occurring spontaneously at rest, and, therefore, 9 of the 10 were considered to have angina decubitus. Three patients were considered hypertensive in that their systolic pressure was above 150 mm. Hg.

TABLE 1.—*Total Cases Explored (Ten)* *

No. Patients	Age, Yr.
1	38
1	47
1	50
2	53
2	54
1	55
1	58
1	63

* All patients were men.

TABLE 2.—*Duration Symptoms* *

No. Patients	Yr.
2	1-2
6	2-5
2	Over 5

* Symptoms: All had typical anginal pain; only one patient did not have pain at rest; hypertension (150 systolic or above) in three patients.

Four patients were considered to have a normal electrocardiogram at rest (Table 3). In six patients, the electrocardiographic tracing made at rest demonstrated abnormalities compatible with myocardial ischemia or questionable infarction. Seven patients developed typical temporary *S-T*-segment depression and depression of the *T*-wave

TABLE 3.—*Electrocardiograms*

	No. Patients
Resting	
Normal	4
Myocardial ischemia	6
Questionable infarct	
	10
With treadmill test	
Developed *S-T* depression & depression or inversion of *T*-wave	7
Developed frequent premature venticular contractions with pain	1
Not done (too much *S-T* depression at rest)	2
	10

TABLE 4.—*Estimation of Disease at Operation* *

Patient	R. Main	L. Main	Circumflex	Ant. Desc.
1	++++	++	++	++++
2	++++	+++	+++	++++
3	++++	++	++	++
4	++	+++	+++	++++
5	+++	+++	+++	++++
6	+++	+++	+++	++++
7	++++	+++	+++	++++
8	++	+++	+++	++++
9	++++	+++	++++	++++
10	++++	+++	++++	++++

* Secondary branches patent in all cases.

with exercise on the treadmill. One patient developed frequent premature ventricular contraction coincident with the onset of anginal pain (Table 3).

Routine chest roentgenograms disclosed a normal heart shadow in five patients and slight to moderate left ventricular hypertrophy in the other five. Coronary angiograms were performed on only one of these patients. The coronary atherosclerosis found at operation was somewhat more extensive than indicated by the angiograms, although the technique of the examination was not entirely satisfactory.

Evidence of extensive disease was found in all major coronary vessels at operation (Table 4). The distal, secondary branches were invariably found to be soft, translucent, and patent. In only one case was slight beading noted in the smaller branches. Certain of these branches distal to areas of complete obstruction of the major vessel were noted to be collapsed at the time of exploration. The left anterior descending artery was found to be most consistently diseased. Complete obstruction of this vessel was encountered in 9 of the 10 patients.

Operation

The operative procedure has been previously described.[10] Briefly, the thorax is opened by a bilateral transsternal incision through the fourth interspaces. Following general palpation and inspection of the coronary arterial system, an area of the right main or left anterior descending artery is temporarily occluded. If no deleterious effect is noted, the vessel is opened longitudinally, the atheromatous core is dissected carefully from the media, and stripped proximally and distally with specially designed instruments until a good blood flow is established from both ends of the opened vessel. The incision is closed with running 000000 arterial nonabsorbable surgical (silk) suture after powdered heparin has been placed in the newly created lumen. Complete heparinization has not been used postoperatively.

Results

In two patients, the heart suddenly dilated and went into asystole while the coronary vessels were being palpated and inspected. In a recent case, myocardial action was reestablished by removing blood from the ascending aorta and pumping it into the distal unobstructed portion of the left anterior descending artery. Endarterectomy was performed in the meantime on the vessel proximal to the point of perfusion. Irreversible asystole occurred during suture of the incision in the artery. One patient did well, despite a persistent hypotension after endarterectomy of the left anterior descending artery, for four days, when pain recurred. The intensity of the pain and hypotension markedly increased by the ninth day after operation. The right coronary artery was endarterectomized on the 10th day after the original procedure, but the patient died two days later in myocardial failure. Autopsy disclosed recent and old myocardial infarcts of the left ventricle. Two other deaths occurred from sudden cardiac dilatation and asystole during suture of the arteriotomy after endarterectomy.

Endarterectomy has been performed on the right main coronary artery alone once and on the left anterior descending artery alone four times. Both arteries were endarterectomized in three patients, including the reoperated-on patient (Table 5).

Of the five patients who have survived, the first was operated upon in December,

TABLE 5.—*Vessels Endarterectomized*

Patient	R. Main	L. Ant. Desc.	Results
1	+	+	Excellent
2	+	+	Op. death
3	+		Fair
4		+	Excellent
5		+	Good
6		+	Fair
7	+ 2d operation	+	Postop. death
8		+	Op. death
9		Vessels not opened	Op. death
10		Stripped with distal perfusion after asystole	Op. death

1957. This patient and Patient 4, operated upon in March, 1958, are considered to have obtained excellent results. They have no symptoms referable to the heart. They are conducting their usual activities, and the treadmill tests have been negative. Patient 5 is considered to have a good result. He was probably the most severely incapacitated of all patients prior to operation, with almost constant pain at rest. *ST*-segments and *T*-wave on the electrocardiographic tracing were depressed at rest. Since operation (April, 1958), he has had attacks of pain during excessive exercise, but he has been able to return to his work as a salesman and the treadmill test has shown improvement in his exercise tolerance.

The two patients who have been considered to have obtained a fair result both demonstrate improved exercise tolerance and diminished chest pain. They both have other disabilities which make evaluation difficult, but there seems to be little doubt that the symptoms of myocardial ischemia have been improved.

Summary

Certain surgical procedures designed to alleviate the symptoms of angina pectoris have been reviewed. Currently, the most promising methods are designed either to increase the intercoronary circulation or to bring additional extracardiac blood to the myocardium.

Our experiences in 10 patients operated upon with the intention of increasing myocardial blood flow by means of direct-vision endarterectomy have been reviewed. In all 10 cases, the extensive coronary atherosclerosis found at operation substantiated the preoperative diagnosis of severe incapacitating angina pectoris. Disease of the major coronary arteries with patent distal vessels was found in each case, and theoretically total coronary blood flow could have been increased by the proposed operation.

Five patients have survived, one for one year three months. All have been improved as judged by their clinical course and by evaluation of the treadmill exercise test.

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Radiography in the Diagnosis of Hepatic Disease

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Through the years the contribution of the radiologist to the definitive diagnosis of liver disease has been limited. A record of his efforts is a list of discouragements and disappointments. There still is no radiographic procedure that easily and quickly provides needed facts in many types of hepatic disorders. In conjunction with their clinical and research colleagues, radiologists will continue, however, to investigate all possibilities that promise better radiologic diagnosis of liver disease.

The widespread use of oral or intravenous cholangiography has aided in diagnosis of conditions affecting the biliary duct. Cholangiography has limitations, however, and as an aid in the diagnosis of liver disease, it is of little value.

Simple Techniques

The ordinary scout film—or preliminary survey—of the abdomen, even though it has limited value, may reveal some useful information about the liver. Often this simple procedure can show the size and shape of the liver, the presence of abnormal masses in the hepatic parenchyma, and calcification.

Roentgenographic evidence of calcification in the right upper quadrant may indicate disease in the kidney, adrenal gland, gallbladder, retroperitoneal region, or liver. Excretory urography, cholecystography, cholangiography, and gastrointestinal studies with barium can help in localizing the calcium. Echinococcus disease can cause calcification in the liver (usually ring-like) occurring in the walls of the cyst (Fig. 1). Tuberculosis may produce calcium in the liver, and this usually is miliary, showing as multiple small areas of calcification scattered throughout the parenchyma of the organ. Hemangiomas produce streaky calcification or phleboliths or a combination of both.

Fig. 1.—Abdomen of a 74-year-old man with calcification in the wall of an echinococcus cyst of the liver.

Wells [1] has reported calcium of a feathery appearance in metastatic lesions in the liver. In the three cases reported by this author, all the primary tumors were carcinomas of the colon. Calcification may be present also in cases of hepatoma; Margulis, Nice, and Rigler [2] report its presence in 3 of 11 cases (Fig. 2).

The radiologic density of the liver is affected by the deposition of certain other materials in certain conditions (for instance, iron in hemochromatosis). Density is relative, however, and difficult to evaluate unless the changes are strong.

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Fig. 2.—Abdomen of an 8-month-old child with enlargement and calcification of liver due to hepatoma.

Hepatic enlargement is difficult to assess. The commonly used relation of liver margin and rib is not always reliable on a roentgenogram. The position of the inferior edge of the liver depends on the degree of inspiration, the body build, the shape of the liver, and many other factors. Estimation of size from the roentgenogram has some value, however, even though it be subjective (Fig. 3). Actual measurement probably is not worth while. Irregularity in outline may sometimes be seen and, when present, is important but usually nonspecific diagnostically.

Fig. 3.—Abdomen of a 2-year-old boy with enlargement of liver due to fatty infiltration.

Fig. 4.—Barium-coated esophagus shows characteristic filling defects of varices.

Sometimes a little information of value can be obtained by roentgenologic demonstration of intrinsic defects or displacement of adjacent organs that can be easily opacified, such as the esophagus, stomach, and colon. Varices can be detected roent-

genologically as filling defects in the lower esophagus (Fig. 4). Schaaf and Wilhelm [3] have reported a high correlation between a fluid level in the duodenal cap and concomitant hepatic or cholecystic disease.

Margulis, Nice, and Rigler [2] have reported that the presumptive diagnosis of hepatoma can be made by roentgenologic methods in the anemic child with a growing mass in the upper abdomen. The basis is roentgenographic demonstration of displacement of anatomic landmarks by the mass. The kidney is discernible as separate from the mass and is pushed back and depressed. The duodenojejunal junction (fixed by the ligament of Treitz) is not pushed forward. This is helpful in excluding the possibility of retroperitoneal masses or lesions in the gastrointestinal tract. The transverse colon is displaced anteriorly and down, and frequently it is found wrapped around the mass. The mass is said to have an undulating lower border and to be indistinguishable from the liver.

A further refinement of this simple approach to the diagnosis of liver disease is pneumoperitoneum, by which these changes in size and contour can be shown more readily than by the ordinary technique. It is time-consuming, however, and the yield does not seem great enough to justify routine use.

Uptake of Dense or Radioactive Substances

It has long been known that the reticuloendothelial cells engulf colloidal particles, and the use of colloidal thorium dioxide in the study of the liver was initiated in 1924. The variation in deposition, and hence in the density, of this material in the liver was thought to be helpful in the diagnosis of early cirrhosis, metastasis, liver abscess, and cyst (Fig. 5). Cirrhosis was evidenced by diffuse mottling or reduced density in the liver. Metastatic lesions were demonstrated as radiolucent zones with a halo of increased density around them, and abscesses were seen as radiolucent zones without the halo of increased density.

Fig. 5.—Abdomen of a 32-year-old man with radiolucent area in liver. Note increased density of liver and spleen due to deposition of Thorotrast.

In recent years we have foregone the use of this technique, since colloidal thorium dioxide (Thorotrast) is not eliminated from the body but rather is permanently deposited in the reticuloendothelial system. Because of its long radioactive life, even a small amount of thorium dioxide could lead to development of necrosis, fibrosis, hematopoietic derangements, and possibly neoplasms.[4] For these reasons, it seems contraindicated except for special studies in older patients.

Attempts have been made also to introduce halogenated fats in emulsified form to be taken up by the reticuloendothelial system and deposited in the liver in much the same way as Thorotrast. Olsson and Ekman,[5] using brominated emulsified sesame oil, found a rich accumulation of contrast substance in the liver and also in other fat depots in the abdomen of white rats. Keith and Briggs [6] used poppy seed oil and bromated olive oil. Beckermann and Popken [7] used emulsified ethyl esters of triiodostearic acid. Gershon-Cohen and McClendon [8] achieved only limited success in the rat, rabbit, and human with iodized, chloriodized, and bromiodized oils, finely emulsified with various emulsifiers in oral hepatosplenography. All of these efforts were abandoned because of untoward reactions.

The search for other substances has continued. Olsson and Ekman [5] have commented on the increase in density of the liver that occurs after treatment of malaria with antimony sodium tartrate. Fischer [9]

has used (in animals) colloidal suspensions of stannic oxide in concentrations of 10% and 20% tin by volume with a particle size of 2μ or less and has obtained satisfactory opacification of the liver. Three hundred fifty milligrams of tin oxide was used per kilogram of body weight. The radiopacity of the liver and spleen reached a maximum in 4 to 6 hours after intravenous injection and persisted for 30 days (not being followed longer). This insoluble colloidal oxide is deposited almost exclusively in reticuloendothelial cells, and it is not radioactive.

Similar results have been accomplished with micronized colloidal gold.

One of the most widespread diagnostic procedures in recent years has been the use of radioactive substances for the localization of liver lesions. One of these is radioactive iodinated human serum albumin (RIHSA), which is concentrated in metastatic growths and granulomas in the liver. The mechanism of the localization or rejection of radioactive substances by the metastatic growth or granuloma is not clear. After injection of RIHSA, the greatest concentration of radioactivity in the hepatic region is in the lesions, and these can be localized with a counter and plotted on an anatomic sketch. Automatic scanning counters may be used to outline the liver substance and record the areas of greatest radioactivity. Generally, a metastatic lesion must be 2 cm. or larger in diameter to be detected. Yuhl and Stirrett [10] reported an over-all diagnostic accuracy of 96% among 187 patients without metastatic lesions and an accuracy of 93% in detecting and localizing metastatic lesions among 53 patients who had them.

Leevy and Greenberg [11] have used this procedure as a localizing device for needle biopsy of the liver. They found that there was considerable increased uptake of I^{131} in the presence of metastatic lesions of the liver and less increase with primary granulomas.

Friedell, MacIntyre, and Rejali,[12] employing an automatic scintillation counter, have investigated the use of radioactive iodophthalein, radioactive rose bengal, and radioactive colloidal gold. These materials are taken up by the liver but rejected by the neoplastic tissues in it. They found that in a 10-cm. thickness the lesion must be 1.5 cm. in diameter to be discovered. Helander and associates,[13] likewise employing an automatic scintillation counter, used radioactive, intravenously injected, colloidal gold. Metastatic lesions in the liver were revealed as spots of reduced density in the scintillograms. Enlargement of the organ and irregularity of its contour could be determined also. These procedures show some promise of being helpful.

Hepatic Angiography

The usefulness of detecting abnormal vascular patterns in the brain by cerebral angiography has led researchers to study the vascular channels of the liver by various methods. Celis and co-workers [14] began investigating the opacification of the circulatory system of the liver in 1948 after a catheter had slipped into the right suprahepatic (right hepatic) vein during angiocardiography. These authors introduced the catheter into the jugular vein and advanced it into the hepatic vein, although entering this vein was often difficult. Bierman and co-workers [15] have shown that the blood supply of neoplasms is derived almost exclusively from the hepatic artery, even though 75% to 80% of the blood supply to normal parenchyma is delivered by the portal system. These investigators used arterial catheters introduced into the brachial or carotid arteries, manipulated them into the celiac or hepatic artery, and then injected iodomethanate (Neo-Iopax) or iodopyracet (Diodrast) directly into the celiac or hepatic artery. They found that the normal liver shows orderly branching and progressive diminution in caliber of the vessels with no gross anastomosis, but in patients with metastatic lesions the vascular pattern is bizarre with pooling and increased vascularity. Therefore roentgenograms of

the opacified vessels can give valuable information regarding the presence or absence of disease of the liver.

Helander and associates [13] have injected the hepatic veins through a radiopaque polythene catheter. The catheter was inserted into the right femoral vein and advanced through the inferior vena cava to the right atrium. An ingenious arrangement of the tip of the catheter made it possible to point the tip in different directions and into the hepatic veins. Small injections of contrast medium aided in determining the location of the catheter. For the examination itself, 15 to 30 ml. of 30% or 45% Urografin was injected, and at least three roentgenographic exposures were made in rapid sequence with a simple cassette changer or an automatic film changer.

In five of six patients with clinically demonstrable metastatic lesions in the liver, identations in the lumen of the large vessels and displacement of the smaller vessels were made visible. This method, like that of Celis and co-workers, is time-consuming and not without danger.

Rigler, Olfelt, and Krumbach [16] were able to visualize the liver by rapid introduction of large amounts of a contrast medium in the aorta above the celiac axis. This procedure is associated with the hazards of aortography.

Moore and Bridenbaugh [17] introduced contrast material into the portal vein during laparotomy. This method permits study of the portal circulation but cannot be employed without laparotomy.

Then splenic portography—opacification of the spleen and liver by percutaneous injection of the spleen itself with a radiopaque medium—was introduced. Hallenbeck and Bruwer [18] used acetrizoate (Urokon) in 70% solution. Normally the medium was diffused throughout the liver. In cases of intrahepatic portal obstruction (as with cirrhosis) and in cases of extrahepatic portal obstruction, the radiopaque substance follows the reversal of flow that takes place and outlines the coronary vein and other branches of the splenic and mesenteric veins, showing their role in providing an outlet for portal blood. Splenic portograms or portal portograms are obtained just before operation on those patients on whom portacaval shunts are planned. Primarily this is done to learn the status of these vessels before the extensive surgical incision is made. Some risk is entailed if this is not done just prior to operation, and the problem of risk is serious if tearing of the splenic capsule takes place. Perisplenic hemorrhage has been reported.

Comment

It is obvious that something better than these procedures is needed. Rigler [19] has suggested the possibility of opacification of the liver by use of contrast substances attached to one of its excretory products, such as urea. This idea should be explored.

The most needed substance is a radiopaque, stable, colloidal suspension which will be taken up by the liver and which will break down in time without toxic effects.

The radiologist's contribution is fragmentary at best. His helpfulness to the clinician is limited by procedures that are inconclusive or maneuvers that are so complex or risky or time-consuming as to be of little practical value. Even with success of some of the complicated and hazardous procedures outlined, only a little information is obtained. It is to be hoped that the contribution of the radiologist to this area of diagnosis will not always be so meager.

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Newer Concepts of Cirrhosis

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The key to progress in our understanding of cirrhosis has been the recognition that the cirrhotic process represents the end-stage of a wide variety of pathological processes of diverse etiology. Accordingly, the term cirrhosis no longer implies a specific clinical or pathological entity but now encompasses a group of diseases that differ not only in etiology and pathogenesis but also in clinical behavior and therapeutic requirements. To review recent developments in our concept of cirrhosis, the topic I have been assigned, would take us into such diverse areas as the morphology of the hepatic changes induced by malnutrition, alcohol, toxins, and infections; the epidemiology, identification, and immunology of viral hepatitis; the biochemistry and histology of collagen formation; the genetics and biological effects of disturbances in the metabolism of galactose, iron, and copper, and many others. Obviously neither time nor my own limitations would permit a comprehensive review of this subject. Accordingly, I shall limit my remarks to a consideration of the role of alcohol in the pathogenesis of Laennec's cirrhosis, a subject that merits special emphasis, since, in this country at least, chronic alcoholism continues to be the leading cause of cirrhosis.

The relationship between chronic alcoholism and cirrhosis has been recognized for over a century and is supported by autopsy evidence indicating that the incidence of cirrhosis is at least six times as high in drinkers as it is in nondrinkers and that the death rate from cirrhosis in many areas is closely correlated with the per capita consumption of alcohol.[1] Particularly impressive are the data showing the parallel decline in the death rates from chronic alcoholism and cirrhosis during the early years of the Prohibition era and the subsequent rise in these rates that has occurred since repeal of the Volstead act.[2] On the basis of autopsy evidence it has been estimated that approximately 8% of chronic alcoholics ultimately develop cirrhosis.[1] Even making allowances for inaccuracies in the collection of these data, it is apparent that only a small fraction of heavy drinkers are subject to cirrhosis. This suggests that there may be differences in susceptibility to the effects of alcohol. Whether these differences are genetically determined or are due solely to environmental factors, such as the diet, is still uncertain.

At the present time most authorities subscribe to the view that the development of cirrhosis in chronic alcoholics is the direct consequence of the faulty dietary habits that often accompany habitual drinking.[3] According to this theory, an excess of alcohol, by providing a large number of calories and by depressing the appetite in other ways, leads to a reduction in the consumption of food, and particularly of protein, resulting in a deficiency of lipotropic substances. These include choline, a constituent of phospholipid; the amino acid methionine, and possibly folic acid and vitamin B_{12}, which, in some species at least, facilitate endogenous choline synthesis. In animals a dietary deficiency of these sub-

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stances leads to fatty infiltration and ultimate fibrosis of the liver. Although many investigators believe that the deposition of fat is directly responsible for the appearance of excess collagen in the liver, others regard these as independent processes.

Recent evidence suggests that the deleterious effects of protein deficiency on the liver may not be due solely to an inadequate supply of choline and methionine.[4] In animals, diets deficient in certain amino acids, like threonine, lysine, and tryptophan, produce a characteristic type of periportal fatty infiltration that is not abolished by lipotropic agents. Moreover, animals maintained on a low protein intake develop hepatic degenerative changes and foci of necrosis that are not seen in pure choline deficiency.[5] These observations may account for the fact that protein supplements are more effective than choline and methionine in the repair of nutritional cirrhosis.

Turning now to the pathogenesis of Laennec's cirrhosis, certain similarities to experimentally induced nutritional cirrhosis are at once apparent. First, it is well known that there is a high incidence of malnutrition in chronic alcoholics with cirrhosis and that dietary supplements of protein are therapeutically effective,[3] in some instances even in the face of continued alcohol consumption. Second, biopsy studies of the liver reveal that, as in the choline-deficient rat, the cirrhotic process begins as a simple fatty infiltration that progresses to the stage of fibrosis and that protein supplements facilitate the removal of such fat and prevent further progression of the fibrotic process; finally, it has been found that a lesion indistinguishable from that of Laennec's cirrhosis is a common occurrence among nonalcoholics in parts of the world where the native diet is deficient in protein.

Judging from such evidence there can be little doubt that nutritional factors play an important role in the pathogenesis of Laennec's cirrhosis. However, there are a number of observations that appear to be inconsistent with the generally accepted view that the effects of alcohol on the liver are due solely to the reduction in food consumption that accompanies excessive drinking. First, alcoholics occasionally develop cirrhosis despite an apparently adequate dietary intake, while, conversely, patients with wasting diseases accompanied by malnutrition are rarely affected. Second, the inflammatory and degenerative changes, including the presence of Mallory bodies, so characteristic of active cirrhosis in the alcoholic are not seen in experimental nutritional cirrhosis. Third, in contrast to the relatively benign character of the lesion in protein-deficient animals, the fatty infiltration and degenerative changes that occur in the alcoholic's liver occasionally give rise to overt hepatic failure and may cause death even in the absence of fibrosis. Finally, it has been demonstrated that under carefully controlled conditions the mere withdrawal of alcohol and the provision of a bare maintenance diet induce significant improvement in the functional and histological status of the cirrhotic liver in alcoholics and that the addition of protein supplements to this regimen is without further benefit;[6] indeed, in short-term experiments similar improvement has been observed in patients given diets virtually devoid of protein.

Recent experimental studies provide additional support for the view that the effects of alcohol on the liver are not due solely to a reduction in food intake.[7] Thus, in the rat it has been demonstrated that alcohol tends to create a relative choline deficiency not only by reducing food consumption but also by adding nonprotein calories to the diet and by a third mechanism which appears to be independent of changes in either food consumption or caloric intake. The fact that the choline requirement is increased by the addition of nonprotein calories to the diet may explain why alcoholics, whose caloric intake is high, develop cirrhosis more readily than patients

with wasting diseases, whose diets may be equally deficient in protein but low in caloric content. Also noteworthy in this connection is the fact that in areas of the world where nonalcoholic nutritional cirrhosis is prevalent, the native diet, while deficient in protein, usually contains an abundance of calories in the form of carbohydrate.

As previously indicated, alcohol also increases the choline requirement by a mechanism unrelated to changes in either food consumption or caloric intake. In the rat, at least, this effect appears to be even more important quantitatively than the other two. Assuming that this mechanism is operative in man, it may explain why some alcoholics develop fatty infiltration and fibrosis of the liver despite an apparently adequate intake of protein. Nothing is known about the mechanism involved in this action of alcohol, but it has been suggested that, since choline may be a factor in the metabolism of acetyl CoA, greater amounts are required when alcohol is oxidized to acetate.[8]

That alcohol may have other subtle effects on the metabolic and enzymatic activities of the liver unrelated to dietary factors is suggested by recent reports that, under the influence of alcohol, transaminase activity is increased in the serum[9] and decreased in the liver,[10] that alcohol depresses the activity of the citric acid cycle in the liver,[11] and that under certain experimental conditions alcohol increases the losses of nitrogen in the urine.[12] Whether or not such alcohol-induced aberrations in enzymatic activity play a role in the pathogenesis of liver disease is still problematical. However, these observations suggest new avenues of investigation and illustrate the important point that in the normal metabolism alcohol there may be other unexpected and possibly deleterious side-effects.

Certain features of the florid type of cirrhosis seen in some chronic alcoholics[13] are not readily explained on the basis of a nutritional or metabolic defect and are not reproducible in experimental animals maintained on deficient diets and a high intake of alcohol. These include a progressive down-hill course often accompanied by fever, signs of hepatic failure that are refractory to dietary and other forms of treatment, and the presence in the liver of extensive necrotic, degenerative, and inflammatory lesions engrafted on an underlying fatty infiltration and/or cirrhosis. The possibility of an intercurrent infection of the liver in such cases has been considered. Attempts to implicate bacteria have generally met with failure. However, the inordinately high incidence of hepatitis virus carriers among chronic alcoholics reported by Neefe[14] suggests that chronic alcoholism may increase the susceptibility to intercurrent infections with the virus or may light up latent infections in carriers. Certainly this possibility merits further investigation.

Related to the problem of infection is the old question of whether or not toxic substances arising from bacterial activity in the intestinal tract play any role in the pathogenesis of alcoholic cirrhosis. Interest in this possibility has been revived by recent reports that in experimental animals broad-spectrum antibiotics that suppress the intestinal flora prevent the development of hepatic fibrosis in choline deficiency[15] and delay the appearance of the hepatic necrosis usually induced by diets deficient in tocopherol and selenium.[16] As provocative as these observations may be, they do not necessarily prove that intestinal toxins injure the liver. Unfortunately, in neither of these experiments was the possibility excluded that the antibiotics used contained a protective factor or that suppression of the intestinal flora deprived the animal of protective substances produced by these bacteria.

In conclusion, a review of the evidence indicates that chronic alcoholism is an important etiological factor in the pathogenesis of Laennec's cirrhosis and that, while the malnutrition often associated with excessive drinking undoubtedly accounts for many of

the effects of alcohol on the liver, there is reason to believe that other, as yet unidentified, mechanisms may be involved.

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Basic Problems of Coronary Disease Today

Occupation and Coronary Heart Disease

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An alternative title to my paper might be "pathology of inactivity" or, even, "occupational hazards of sedentary and light work." Technical development has involved a drastic reduction of physical activity in work, in transportation, and probably in leisure too. Indications are that this trend will continue and increase. Up to now, most investigations of it as a health problem have related to activity and inactivity of jobs. Some current epidemiologic studies in the Social Medicine Research Unit of the British Medical Research Council will be reported.[1]

Coronary Heart Disease in London Busmen

Studies of coronary heart disease among London busmen begun in 1949 showed almost at once that the drivers suffered more commonly from sudden death due to coronary heart disease than the conductors (ticket collectors) of these double-decker vehicles.[2] Data have now accumulated for 10 years (Table 1). This shows that, under 50 years of age, drivers have three to four times the "sudden death" rate of the conductors. The drivers have more coronary heart disease as a whole throughout the 35 to 64 age group, but the main occupational difference is in the most malignant form of the disease among the younger men. Similar observations were made in government service. Men in three sedentary jobs, office clerks, minor officials, and telephone (switchboard) operators, each had far more rapidly fatal cardiac infarction under 50 years of age than the physically active postmen. The British postman walks and cycles for about two-thirds of his time on the job. Generally, light workers were found to have higher coronary death rates than physically active workers, and active

TABLE 1.—*Coronary Heart Disease in London Busmen—"Sudden Death" as First Clinical Manifestation* *

Ages	Drivers	Conductors
35-49	0.56	0.17
50-64	1.9	1.2

* Average annual rates *per 1,000*, 1949-58.
Drivers, 133,000 man-years; conductors 80,000 man-years.

TABLE 2.—*Coronary Heart Disease in Men of Different Occupations—Mortality in England and Wales*

Social Class	Ages 45-54 Occupation			Ages 55-64 Occupation		
	Light	Active	Heavy	Light	Active	Heavy
I	176	—	—	568	—	—
II	167	118	—	515	404	—
III	173	137	111	529	444	422
IV	153	121	116	422	380	341
V	175	145	91	424	409	283
All	173	135	102	528	422	339

Death rates *per 100,000*, 1949-53.
No. 420, International Statistical Classification of Diseases, Injuries and Causes of Death, World Health Organization, 1948.
Social Class I=leading professions, officials and business, e.g., physicians, ministers of religion.
Social Class II=lesser professions, officials and business, e.g., dock and harbor officials, teachers.
Social Class III=skilled workers, e.g., radio and telegraph operators, musicians.
Social Class IV=part-skilled workers, e.g., farm laborers.
Social Class V=unskilled workers, e.g., building laborers.

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workers higher than heavy workers (Table 2), i.e., it is not merely a matter of "sedentariness."

Corroboration from Pathology

A national necropsy survey carried out in Great Britain during the period 1954-56 showed that coronary heart disease was commonest in light workers throughout the 45 to 70 age group.[3] This seemed to be true of fatal coronary heart disease itself. More interesting, among 3,800 deaths from some other cause than coronary heart disease, e.g., accidents or cancer, ischemic fibrosis of the myocardium as an incidental finding at postmortem was commonest in light workers. Again, the main occupational difference was in the frequency of the severest disease, the large healed infarct (1.5 cm. in diameter and usually transmural) in early middle-age (Table 3). In fact, this was as common in light workers aged 45 to 54 as in heavy workers aged 65 to 70. Thus the pathologic picture was similar to the clinical picture previously found.

Pathogenesis

Coronary Atherosclerosis.—The amount of disease of the walls of the coronary arteries was found in this survey to bear little relation to occupation. However, severe narrowing of the coronary arteries and frank coronary thrombosis, were commonest in light workers. This suggestion that *mural atheroma* behaves differently from *coronary occlusion* in regard to an environmental factor (occupation) is interesting. Historical study suggests that disease of the coronary walls was very common before the first world war and that the occlusive process alone has increased during the present century and underlies the "modern epidemic" of coronary heart disease.[1]

Essential Hypertension.—Hypertension without evident primary cause is particularly common in light workers. This has been observed both in a current clinical survey[4] of London busmen (e.g., Table 4) and in the national necropsy survey already mentioned. Moreover, hypertensive light workers seem particularly liable to coronary heart disease, and again particularly at 45 to 59 years of age, judging from the postmortem findings in the necropsy survey. In this, Table 5, hypertensive light workers showed about three times more ischemic myocardial fibrosis than other workers

TABLE 3.—*Ischemic Fibrosis of the Myocardium in Men of Different Occupations—Deaths from Some Other Cause Than Coronary Heart Disease at Ages 45-59*

Pathology in Myocardium	Occupation		
	Light	Active	Heavy
Large healed infarct	2.3	1.3	0.5
Focal, patchy fibrosis, and lesser infarcts	7.7	4.3	3.4
All types of ischemic fibrosis	10	5.5	3.9

Prevalence rates of ischemic scarring %.
1,800 deaths from injuries, infections, malignant disease, cerebrovascular conditions, etc., in the national necropsy survey, Great Britain, 1954-56.

TABLE 4.—*High Blood Pressure in London Busmen*

Ages	Systolic over 180		Diastolic over 105	
	Drivers	Conductors	Drivers	Conductors
40-49	8.8	2.1	3.5	0
50-59	12.5	6.8	12.5	4.3
60-64	16.4	14.8	12.3	11.1

% with these "casual" readings.
Sample of 640 men, 1956-59.
Clinical survey of London busmen.[4]

TABLE 5.—*Ischemic Fibrosis of the Myocardium in Relation to Hypertension and Occupation—Men, Aged 45-59*

		Occupation		
		Light	Active	Heavy
Hypertension	Essential hypertension present	24	9.4	2.2
	No record or evidence of hypertension	6.6	3.8	3.7

Prevalence rates of ischemic scarring %.
All types of ischemic myocardial fibrosis combined. These are the 1,800 deaths from some other cause than coronary heart disease in the national necropsy survey already described in Table 3, excepting that the small number of cases of secondary (mostly renal) hypertension have been omitted.

TABLE 6.—*Blood Lipids of London Busmen*

Ages	Total Plasma Cholesterol Mg. %		Lipoproteins					
			Sf 0-12		Sf 12-20		Sf 20-400	
	Drivers	Conductors	Drivers	Conductors	Drivers	Conductors	Drivers	Conductors
40-49	249	228	338	310	70	53	151	107
50-59	254	238	341	313	62	41	176	89
60-64	262	246	346	344	54	50	124	98

Average values for age-occupation groups.
Courtauld Institute of Biochemistry, Middlesex Hospital, London.
Numbers of men in the samples reported above range from 22 to 77 for the cholesterol estimations, and 30-114 for Sf.

with hypertension and about six times more than all without hypertension; i.e., there was a gross excess also of "focal" fibrosis of the myocardium, the diffuse patchy lesions associated with hypertension, in the hypertensive light workers. This was the situation in necropsies where the main cause of death was not coronary heart disease itself. Furthermore, fatal coronary heart disease itself was also particularly common in hypertensive light workers; that arising on moderate or little coronary atheroma showing an even greater excess than the remainder.

Blood Lipids.—Results are now beginning to come in of the blood lipid study being made for us by the Courtauld Institute on samples of working (presumably healthy) London busmen (e.g., Table 6). Drivers' levels are higher, particularly in the ultracentrifugal analysis. Crude information on diet reveals no gross qualitative differences between drivers and conductors; a systematic dietary survey in which busmen in their 40's weigh their food for a week is now being made.

TABLE 7.—*Shape of London Busmen*

Ages	Trouser Waist, 38 in. and More		Trouser Waist, 32 in. and Less	
	Drivers	Conductors	Drivers	Conductors
25-29	9	2	52	73
30-34	11	3	46	55
35-44	17	8	38	54
45-54	32	13	18	40
55-64	44	21	11	29

% of men in each age-group with these measurements.
Samples of 4,200 men, 1954 and 1958.

There is no evidence so far that men with high blood lipid values have particularly high blood pressures or that men with high pressures have particularly high lipids; i.e., these two phenomena are independent of each other. Since both are common, they do of course coincide in some persons, with ominous implications.[5] A study is now being made of this by age and occupation.

Obesity; Constitution; Self Selection for Jobs.—A sample of uniforms in London Transport showed (among other like observations) that drivers more often had trouser waists of 38 in. and above, conductors more often of 32 in. and less (Table 7). These differences were just about as clear at 25 to 29 years of age, very early in the work career, as at 55 to 64; i.e., very likely, different men select different jobs. The accuracy of the tailors' waist-bands has been confirmed in the clinical survey (and skinfolds also are thicker in drivers than conductors, Table 8). So far this observation on the differences in physique is not explaining much, Table 9. Fat, young drivers have five times the sudden-death rate of conductors who are not fat—but all drivers, including the thin, have higher

TABLE 8.—*Skinfolds in London Busmen*

Ages	Drivers	Conductors
40-49	44.2	33.3
50-59	47.0	37.0
60-64	44.1	35.0

Average sum in mm. of 3 skinfolds-triceps, subscapular, suprailiac.
Sample of 500 men. Clinical survey of London busmen.

TABLE 9.—*Sudden Death in London Busmen Aged 35-49 in Relation to Their Shape*

Trouser Waist	Drivers	Conductors
38 in. and more	0.97	—
34-37 in.	0.46	0.19
32 in. and less	0.76	0.19

Average annual rates *per 1,000*
Drivers, 1953-58; conductors, 1949-58.

rates than corresponding conductors. The results are even less interesting on analysis by jacket breast. Manifestly, physique is not the crucial factor in producing the occupational differences reported. In the clinical survey, measurements are being taken to enable each man to be somatotyped. The relations between constitution and environment, between what men are, do, and become now present some of the most fascinating problems in the field of chronic disease.

Comment

All these studies seem to be adding up to the notion that physical activity/inactivity is a general factor of cardiovascular health in middle-age, being related to the frequency of coronary heart disease and coronary occlusion, to blood pressure and blood lipid levels, to obesity, and possibly also to diabetes. Coronary heart disease may therefore be in some measure a deficiency disease. Just as we are accustomed to think of the physiology of exercise, we should be thinking too about the pathology of inactivity, of disuse. Meanwhile, it is not possible to estimate the size and importance of this factor in relation to other factors in cardiovascular health and disease in middle-age, and its connections with caloric balance, lipid homeostasis and the blood pressure in this connection need to be elucidated. Phylogenetically, the increased sedentariness of modern living makes no sense. Maybe it is the mesomorph who suffers most from the disuse of his large muscles; maybe less effective production of coronary collaterals is one of the biologic consequences of this social revolution; maybe the loss of a channel for discharging aggressive drives is finding us out.

Prevention Through Leisure Activities?—The clock cannot be turned back and physical activity returned to work. Once again, as with so many problems of modern public health, the future seems to lie in the more constructive use of our increasing leisure. Little attempt has yet been made to discover whether there is any relation between physical activity apart from work and health during middle age; such studies are badly wanted.

Strain of Occupations and "Stress"

There is growing interest in the possibility that nervous and social strain in work induces in some men stress reactions which are connected with cardiovascular disease in middle age. The last Table shows the occupations with the highest mortality from coronary disease.[6] All are "light" occupations, physically, but there is clearly a wide range of coronary death rates among light occupations which is hidden in the averages for all such occupations given in the first columns of Table 2. The radio and telegraph operators' experience could be readily explained in terms of "stress" and, perhaps, some of the others. However, it is obviously not at all simple. Thus business managers showed a ratio of 112 compared

TABLE 10.—*Occupations with Highest Mortality[1] from Coronary Heart Disease—Men Aged 20-64, England and Wales, 1949-53*

Occupation	Standardized Mortality Ratio
Radio and telegraph operators	207
Roman Catholic priests and monks	193
Dock and harbor officials, etc.	175
Chemists (scientists)	169
Physicians	159
Commercial brokers, agents, etc.	156
Clergymen (Church of England)	153
Musicians	151
Managers and directors in communications (mainly post office)	149
Garment workers	149
Telephone operators	144
All men, the average	100

These are not rates, as in Table 2, but ratios of the national average rate, allowance having been made for the difference in age structure between occupations.

with an average for all men of 100, and commercial company secretaries showed a ratio of 115; both these occupations would probably be called "executives" in the U.S.A. Office clerical workers, however, had a ratio of 132. Bureaucrats did surprisingly well; the top public officials' ratio was 94. The figure for foremen, a particularly interesting group psychologically and sociologically, was 99, just average. None of the active and heavy occupations approached the high ratios of Table 10. The lowest ratio of any occupation was for agricultural workers, 55, and it did not seem to make any difference whether these men had been farmers or farm laborers.

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Increased Incidence of Coronary Heart Disease in Women Castrated Prior to the Menopause

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There is increasing evidence to suggest that multiple factors, including heredity, occupation, diet, stress, and preexisting hypertension, diabetes mellitus, hypercholesterolemia, and obesity, are involved in the pathogenesis of coronary heart disease. It has also been observed for many years that women have less coronary disease than men. As long ago as 1803, William Heberden recorded that there were only 3 women in nearly 100 patients with pectoris dolor (angina pectoris).[1] In a series of 30,000 autopsies, Clawson found a male-female ratio of 8:1 among patients with coronary sclerosis without hypertension.[2] Clinical studies of coronary heart disease have also shown a sex difference, Levy and Boas[3] reporting a male-female ratio of 4.9:1, and Master, Dack, and Jaffe[4] reporting 3.4:1. These studies have confirmed the observation that women have a decreased incidence of coronary atherosclerosis as compared with men.

Even more striking is the rarity of this disease in women under 40 years of age. Of 95,000 such women admitted to the Mayo Clinic in an 11-year period, there were only 27 patients with coronary heart disease.[5] In two separate studies, each of 100 patients under 40, White and co-workers found only 4 women in the first group[6] and 3 in the second.[7] In young women, when estrogen production is high, the serum lipids are normal, i.e., low total cholesterol, cholesterol/phospholipid (C/P) ratio, and β-/α-lipoprotein cholesterol (β/α) ratio.[8] Decreased atherosclerosis has been demonstrated in cancer of the breast associated with ovarian stromal hyperplasia and hyperestrogenism.[9] Furthermore, abnormal serum lipids found in women with coronary disease have been reversed on adequate estrogen administration.[10] These facts suggest a possible relationship among estrogen, normal serum lipids, and a relative immunity to coronary heart disease.

An increase of serum lipid levels[11] and a higher incidence of coronary heart disease after the menopause have been documented in several studies.[12-14] Anatomic studies have shown less coronary atherosclerosis in women with intact ovaries compared with oophorectomized women.[15,16] These investigations suggested that this accelerated atherogenesis required at least five years to become apparent anatomically. In the present study it was of interest to investigate not only the role of normally functioning ovaries in the prevention of coronary heart disease in younger women but also the deleterious effects of early castration.

Materials and Methods

A record review was made of all patients who underwent bilateral oophorectomy prior to age 45 at The Memorial Hospital during the 20-year

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TABLE 1.—*Source of Patient Material*

Group	Castrate	Control
Examined	155 (36.6%)	152 (32.9%)
Refused examination	28 (6.6%)	45 (9.7%)
Untraceable	153 (36.2%)	176 (38.1%)
Contacted, not yet examined or not yet contacted	80 (18.9%)	87 (18.8%)
Died	7 (1.7%)	2 (0.4%)
Total	423	462

period, 1936 to 1955. A similar study was made of patients who underwent hysterectomy prior to age 45 without bilateral oophorectomy during the same period of time to serve as a control group. A public health nurse then traced as many of these patients as possible in order to recall them for a complete cardiovascular evaluation, including serum lipid studies. Table 1 shows that of the 423 women in the castrate group, 153 (36.2%) were untraceable and only 28 (6.6%) refused examination; 7 (1.7%) had died; 155 (36.6%) were examined, and the remaining 80 (18.9%) could not be examined because of their work schedules or have not yet been contacted. There were 462 persons in the control group: the proportions of examined and unexamined women were similar to those of the castrate group, but there were only two deaths.

In order to study the effects of estrogen deprivation, 53 of the 155 castrated subjects who had been on adequate estrogen replacement therapy were eliminated from the study, leaving 102 who had little or no replacement. For the same reason 40 of the 152 control women were deleted from this study, leaving 112 subjects who also had not received estrogen treatment. In order to assess the role of ovarian estrogens in the prevention of atherosclerosis, emphasis was placed on the study of the prematurely castrated group without significant postoperative estrogen therapy and the directly comparable subjects with one or both ovaries intact. As an additional control, data on the prevalence of coronary disease in 700 women who had not had hysterectomy or oophorectomy were obtained from the Heart Disease Epidemiology Study, Framingham, Mass., through Dr. T. R. Dawber, Medical Director. After age-adjustment, this prevalence was compared with those in the castrate and control groups of the present study.

A detailed medical history and a physical examination were carried out on each patient, using a modification of the standard form developed at the Heart Disease Epidemiology Study. Laboratory examinations included an electrocardiogram, chest x-ray, complete blood count, fasting blood sugar, nonprotein nitrogen, urinalysis, and vaginal smear stained by the Papanicolaou technique as an estimation of estrogen effect. The absence of cornified epithelial cells, with or without precornified cells, was classified as minimal estrogen response. Postabsorptive serum was obtained for analysis of total cholesterol and phospholipids[17] and ultracentrifugal separation of the α- and β-lipoproteins with determination of the cholesterol content of both fractions.[10] The cholesterol/phospholipid and β-/α-lipoprotein cholesterol ratios were derived from these results.

Results and Comment

Premature castration results in an increased prevalence of clinical atherosclerosis, including coronary heart disease, as shown in Table 2. In the castrate group there were 16 patients with definite coronary heart disease, 15 with angina pectoris and 1 with a previous myocardial infarction. In contrast, there were only five such patients, four with angina pectoris and one with a myocardial infarction, in the control group. This increased prevalence in the castrate group was statistically significant by the χ^2 test ($0.01<P<0.025$). When peripheral vascular disease is also included as a manifestation of clinical atherosclerosis, 3 such additional patients in the castrate group increase the total with definite disease to 19, decreasing the above probability of chance occurrence to less than 1 in 200 ($P<0.005$). In both castrate and control groups there were 3 patients with question-

TABLE 2.—*Prevalence of Atherosclerotic Disease in Castrate and Noncastrate (Control) Women*

Group	No.	AP	MI	PVD	Total Definite Atherosclerotic Dis.	QAP	Total
Castrate	102	15	1	3	19	3	22
Control	112	4	1	0	5	3	8
Statistical significance		$0.01<P<0.025$			$P<0.005$		$0.005<P<0.01$

AP indicates angina pectoris; *MI*, myocardial infarction; *PVD*, peripheral vascular disease; *QAP*, questionable angina pectoris.

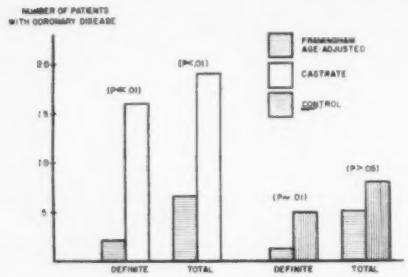

Fig. 1.—Prevalence of coronary disease in castrate and noncastrate (control) women *vs.* expected prevalence in intact women based on Framingham study.

able angina pectoris, and if these were to be included, the difference in the final totals, 22 in the castrate and 8 in the control group, was highly significant ($0.005<P<0.01$). Since it is well known that coronary disease in women under 50 is rare, except in association with hypertension or diabetes mellitus,[3] patients with either of these conditions at the time of operation were excluded, and the prevalence of coronary disease was recalculated. There were 92 subjects in the castrate group who had normal blood pressure and did not have diabetes at the time of operation. Of these 12 had developed definite coronary disease. In contrast, of the 100 originally normotensive, nondiabetic control subjects there were only 3 who had developed coronary disease, again resulting in a statistically significant difference between the groups ($0.01<P<0.025$). Since none of the three patients with peripheral vascular disease in the castrate group was hypertensive or diabetic at the time of operation, their addition to those with coronary disease resulted in an even more highly significant difference between the castrate and control groups ($P<0.005$). Thus the elimination of preexisting hypertension and diabetes mellitus did not greatly alter the increased prevalence of clinical atherosclerosis in these prematurely castrated women.

A comparison of the number of patients with coronary disease in each group was made with the number expected on the basis of the women examined in the Heart Disease Epidemiology Study, as shown in Figure 1. Because of a small difference in the age composition of the castrate and control groups of this study, a separate age-specific expected prevalence was calculated for each group. "Definite" refers to unequivocal coronary disease, while "total" includes questionable angina pectoris. It is of interest that, with use of the Framingham group as a control for the castrate group, the difference in prevalence of coronary disease was highly significant, whether definite or total numbers were considered. Similar comparison of the control and Framingham groups revealed that when total numbers were considered, no significant difference in incidence of disease was found, although there was a significantly greater prevalence of definite disease in the control group. This discrepancy emphasizes the difficulty in obtaining uniform clinical evaluation of patients with angina pectoris, a disease manifested symptomatically without reliable objective changes during much of its course. The predominance of angina pectoris in this study as a manifestation of arteriosclerotic heart disease confirms the previously reported results from Framingham.[18]

Serum lipid studies in the control and castrate groups are tabulated in Table 3.

TABLE 3.—*Average Serum Lipid Levels in Castrate and Noncastrate (Control) Women in the Fifth and Sixth Decades of Life* *

Age at Exam.	Group	No.	Chol.	PL	C/P	α-Chol.	β-Chol.	β/α
41-50	Control	54	220	195	1.13	53	155	3.2
	Castrate	43	*264*	*219*	1.21	58	*192*	3.6
51-60	Control	50	265	*232*	1.15	56	200	3.7
	Castrate	30	272	232	1.18	54	211	4.1

* *Italics* denote statistically significant differences ($P\gtrsim0.001$). *Chol.*, cholesterol; *PL*, phospholipids.

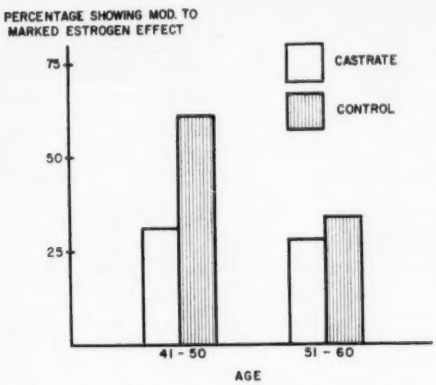

Fig. 2.—Estimation of endogenous estrogen output by cytologic evaluation of vaginal smear.

Since there were so few women outside the 41-to-60 age group at the time of examination, only data for the 41-to-50 and 51-to-60 decades are considered. In the fifth decade, serum cholesterol, phospholipids, and β-lipoprotein cholesterol levels were all higher in the castrate than in the control group, and these differences were highly significant ($P \leqq 0.001$). But in the sixth decade this difference in the serum lipid levels was not seen. The similarity of the lipids in the younger castrates and in both the older groups suggests that the protective role of intact ovaries wanes after the natural menopause.

The results of cytologic studies of the vaginal epithelial cells, shown in Figure 2, lend support to the concept of a relationship between functioning ovaries and the maintenance of relatively normal serum lipids. Of the control subjects (those with one or both ovaries intact) in the younger decade, 61% had moderate to marked estrogen response, based on counts of both precornified and cornified cells. In contrast, 31% of of the younger castrates, 34% of the older controls, and 28% of the older castrates showed a similar response. It is surprising that, in the absence of functioning ovarian tissue, there is any significant estrogen effect on the vaginal epithelial cells. The synthesis of estrogens by the adrenals must be considered as a possible explanation for this appreciable estrogen effect in 30% of these castrated women.

In Table 4 are tabulated the average serum lipid data of the 102 persons in the castrate group, separated into a clinically normal series of 83 and one of 19, 16 of whom have coronary disease and 3, peripheral vascular disease. There was a suggestion of "worsening" of the serum lipids in the diseased persons, namely, an increase of serum cholesterol, C/P ratio, β-lipoprotein cholesterol, and β/α ratio, with a decrease in the α-lipoprotein cholesterol. These changes are in the same direction as those previously reported from this laboratory.[8] The results of this earlier study were based on the serum lipid values of 39 castrated women with coronary disease and 39 age-matched, castrated, clinically normal persons in which there was a significant elevation of both the C/P and β/α ratios in the coronary group.

In order to investigate whether factors other than premature bilateral oophorectomy might have played a role in the pathogenesis of increased atherosclerosis in the castrate group, additional information, such as age, years elapsed since operation, nationality, and the incidence of hypertension, obesity, and diabetes were studied. In Figure 3 the age distribution at the time of examination of the two groups is shown to be similar, as are the average ages of the castrates (50.4 years) and the controls (49.0 years). Also, as shown in Figure 4, the average elapsed time since operation in the two groups was nearly identical, 10.9

TABLE 4.—*Average Serum Lipid Levels in Castrate Women: Atherosclerotic* vs. *Normal*

	No.	Chol.	PL	C/P	α-Chol.	β-Chol.	β/α
Clinically normal	83	264	221	1.20	56	198	3.8
Coronary + PVD	19	282	231	1.23	52	210	4.3

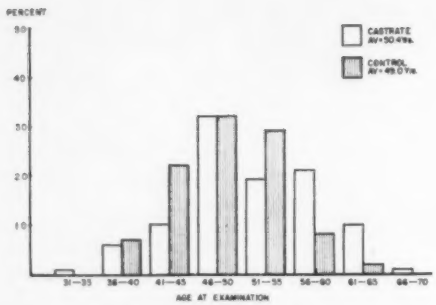

Fig. 3.—Age distribution of castrate and noncastrate (control) women at time of examination.

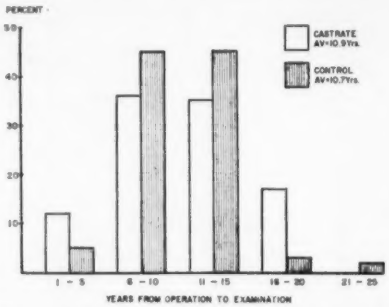

Fig. 4.—Elapsed time between pelvic surgery and examination in castrate and noncastrate (control) women.

and 10.7 years, respectively, with again a similar distribution. The most frequently represented nationalities were those of the British Isles (English, Scotch, and Irish), French Canada, and Scandinavia, accounting for 64% of the total in the castrate and 77% in the control group. No other nationality accounted for more than 5% of the total number in either group.

Obesity greater than 20% was found to be present in 38% of the castrate and 32% of the control group. The baseline for the ideal weight at each height was calculated from the mean weight for women of medium frame according to figures from the Metropolitan Life Insurance Company Statistical Bureau, 1943. The apparent difference in incidence of obesity was not statistically significant. Furthermore, 46% of both groups were normal or, in a few instances, underweight.

In Table 5 a comparison is made of the frequency of several findings that often are seen in association with clinical atherosclerosis. Three categories are compared, the control and castrate groups from which those with definite disease were excluded and the women with vascular disease drawn from the castrate group. The incidence of hypertension, retinopathy, arcus senilis, and enlarged heart by x-ray was higher in the castrate group and even greater in those with vascular disease. Diabetes mellitus occurred more often in the diseased castrates. Since these trends, although suggestive, were not significant on statistical analysis, their final evaluation must await the completion of the study of more patients.

TABLE 5.—*Comparative Incidence of Associated Findings*

Groups	No.	% HBP	% Abn. Ret.	% Arc. Sen.	% E.H.	% D.M.
Normal control	107	36	19	12	8	4
Normal castrate	83	45	26	17	15	4
ASHD, PVD castrate	19	58	47	41	16	21

ASHD indicates arteriosclerotic heart disease; *HBP*; hypertensive, *Abn. Ret.*, abnormal retinal findings; *Arc. Sen.*, arcus senilis; *E.H.*, enlarged heart; *D.M.*, diabetes mellitus.

TABLE 6.—*Serum Lipids of Groups Shown in Table 5*

Groups	No.	Chol.	PL	C/P	α-chol.	β-chol.	β/α
Normal control	107	243	212	1.15	54	178	3.5
Statistical significance, normal control vs. normal castrate		P<.01	NS	.01<P<.05	NS	P<.01	NS
Normal castrate	83	264	221	1.20	56	198	3.8
Castrate with ASHD or PVD	19	282	231	1.23	52	210	4.3

The serum lipids of the same groups are shown in Table 6.

The significantly higher C/P ratio of the normal castrates was chiefly due to an increase of the serum cholesterol. This resulted from an elevation of the β-lipoprotein cholesterol, with little or no change in the α-fraction. Similar differences of the serum lipids between the normal and diseased castrate groups were only suggestive, proving to be without statistical significance.

Summary

Bilateral oophorectomy prior to the natural menopause resulted in an increase of atherosclerosis, manifested clinically as coronary heart disease and peripheral vascular disease, as compared with a similar group of women who underwent hysterectomy without castration.

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Spurious Heart Disease

A Problem in the Management of Coronary Disease

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Spurious heart disease resulting from an erroneous diagnosis and consequent treatment for nonexistent coronary artery disease is common. While spurious coronary disease does not result in death, it causes unnecessary restriction of physical activity and diet, expensive diagnostic procedures and therapy, and loss of time from work. It frequently produces a type of disability which is more detrimental to the patient, his family, and his community than true coronary artery disease.

Numerous factors are responsible for the origin and aggravation of spurious coronary disease. They relate to the nature of coronary disease, the patient, and the attending or consulting physician.

The incipient and subtle nature of coronary disease, the multiple symptoms by which it may be manifested, and the fact that if often defies diagnosis until an acute coronary occlusion occurs are features which produce anxiety on the part of the patient and overdiagnosis and false diagnosis by attending physicians. Other features of the disease which have increased an awareness and apprehension on the part of the public exceeding that of any other form of heart disease are (1) the recognized frequency of coronary disease in our adult population, especially as a cause of sudden death in one in apparent excellent health; (2) the publicity which this disease has received in the medical and public press, and (3) the importance that has been given it in fund-raising campaigns and federal appropriations for our fight against heart disease.

There are many ways in which this combination of the nature of the disease, the patient, and the physician enter in the development of a spurious disease. From a patient's standpoint there is the anxiety and apprehension engendered by the frequent press reminders of its threat. The oftenquoted proverb, "A little knowledge is a dangerous thing," applies, and yet the opposite appears to be equally true, as we often find spurious heart disease to be an important problem in physicians themselves and the highly educated laymen.

The chief contributions which the patient makes to the development of spurious coronary disease are by (1) possessing basically a neurotic disposition, (2) being subjected to an influencing situation, (3) actual malingering, and (4) honest self-diagnosis by relating symptoms arising from other systems to that of the heart. There was a time when this latter source of spurious disease was of minor importance, as it was of concern only in the management of neurotic

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persons, especially those with fixed cardiac neuroses. However, today when the "do-it-yourself" campaign is popular, even in medical care, many persons practice self-diagnosis and self-treatment in the form of restriction of diet and physical activities or even self-medication. There is a movement underway to permit pharmacies to dispense nitroglycerin without prescriptions for the self-treatment of self-diagnosed angina. Persons have presented themselves to surgeons for operations to cure self-diagnosed coronary disease. At times they have been accommodated without appropriate study.

I have never evaluated a person with symptoms or findings which were considered to be coronary disease by himself or another physician in whom I believed there was genuine malingering. Some were instances of honest self-diagnosis, but the majority were neurotic persons misdiagnosed as having angina, "heart attacks," or abnormal electrocardiograms by previous physicians. The anxiety state was often increased with the frequency and number of examinations and at times was greatly aggravated by problems and situations concerned with secondary gain. These included threats to interpersonal security, temporary relief from responsibilities or pressures of an undesirable assignment, or that of obtaining attention and sympathy from their family and friends. In others, disability retirement, veteran's compensation, or other monetary compensation played a great part in the severity of symptoms. This is not true malingering. There are only a few instances of proven malingering in coronary disease in medical and legal records in spite of repeated suspicions in individual cases. The organized insurance racket,[1] exposed in New York City in 1937, is one such example. In this instance symptoms of coronary disease were successfully malingered in persons who were schooled by unscrupulous physicians, supported by drug-induced changes in their electrocardiograms, and unwittingly confirmed by unsuspecting prominent cardiologists who were called in for consultation at an appropriate time. An editorial comment[2] published on this subject contains these statements:

> In all the annals of criminal ingenuity with a medical tinge there has seldom been a more cold blooded, heartless, or vicious scheme than the one now described. The manner in which the patients who permitted themselves to be inveigled into the rackets were first physically exhausted and then perhaps permanently damaged by the use of drugs; the manner in which competent, ethical physicians without even a hint of suspicion were drawn into the scheme so that their prestige and their names might be abused for the benefit of swindlers, and the manner in which the most modern scientific methods of diagnosis were employed in order to give the appearance of scientific authenticity to the reports—all these are unique in criminal annals.

The details of this racket revealed how easily spurious coronary disease could be produced in patients by malingering as well as the various ways in which physicians may become involved.

Physicians have become increasingly aware of the difficulties in the recognition of coronary artery disease and in rendering an accurate prognosis after it is recognized. The inability to recognize the disease in many instances until a fatal or near-fatal complication occurs has created a feeling of inadequacy in the conscientious physician. There is a tendency to overcompensate for this inadequacy of the medical profession. Studying a patient in this state of mind the physician is likely to err on the side of an organic diagnosis. This contributes to the development of spurious heart disease by creating what is commonly known as iatrogenic heart disease. Iatrogenic disease is by definition an illness that supposedly stems from or is aggravated by medical treatment.[3] It is usually considered that it is something that the physician has said or done that has frightened the patient into a state of chronic anxiety about his health. The diagnosis of iatrogenic heart disease is popularly attached to a persistent cardiac neurosis presumed to have been caused by a physician's carelessness or callousness in explaining the heart symptoms or minor heart finding to the patient. In most instances, however, where the patient with

so-called iatrogenic heart disease has been carefully studied, it is found that his difficulty is due more to omission than commission on the part of the physician. Experience indicates that the symptoms develop primarily in those patients with preexisting anxiety neurosis. As Hart further states,[3] "these patients who develop iatrogenic disease have a personality defect and the physician plays an iatrogenic role simply by being there at the time the individual seeks medical attention." Ebaugh,[4] in speaking of this part of the physician's responsibility in this problem, lists "failure to recognize existence of emotional factors in illness; inability to treat minor emotional disorders if recognized; and lack of awareness of the role that physician's feelings, attitudes and behavior play in the cause of sickness." Hart again states,[3] "it is attitude, not his time that the patient mainly needs from a physician at first."

Many years ago Houston,[5] in discussing the doctor himself as a therapeutic agent, stated, "the scales may be quite often favorably weighted by the attitude of an interested physician whatever his inclination or specialty."

A recent study designed to evaluate the part of the patient and the physician in the cardiac symptom formation of the anginal syndrome, especially in patients with normal hearts, suggested that only rarely did the physician provoke the earliest symptom of the disorder.[6] In this study, as in my own experience, the physician did occasionally play an active part in the production of symptoms, in others he definitely aggravated the fears and disability by his remarks and attitude. The physician also frequently augments preexisting abnormal anxiety referable to the heart by evincing doubt about the diagnosis, by repeating previously normal laboratory tests, by demonstrating excessive concern over the patient's symptoms, or by recommending restriction of activity. A physician cannot adequately reassure a patient that his heart is normal and that he does not have coronary disease if he himself has a fear that the patient might have heart disease. He cannot help reflecting that belief in his attitude toward the patient. Such superficial and insincere reassurance by the physician does more harm than good to the patient. In most instances, the patient, continuing his fears, goes to another physician or consultant, convinced that he has heart disease.

Numerous studies and opinions clearly indicate that it is the physician's attitude toward the patient's symptoms and his failure or omission to recognize the underlying personality defect and neurosis that produces the so-called iatrogenic coronary disease rather than what he states to the patient.[7-9] Aring [10] describes the importance of an empathetic understanding and attitude rather than a purely sympathetic attitude toward the patient.

The next manner by which the physician may be responsible for the production of spurious coronary disease is definitely one of commission. This is the result of misinterpretation of a given symptom or finding as clearly indicating coronary disease. Factors contributing to this error in diagnosis are many. Unfamiliarity and inexperience with coronary disease is a factor. Failure to take the time to obtain a good history and overdependence on laboratory procedures and instrumentation leads to errors and thereby create instances of spurious coronary disease.

In his awareness of coronary disease, the physician too often identifies a symptom such as any anterior chest pain or discomfort as a probable manifestation of coronary disease. While it is important to consider coronary insufficiency or angina as a possibility, especially if the patient is in the so-called coronary age group, one must keep in mind in the differential diagnosis the innumerable noncardiac and noncoronary conditions which give rise to anterior chest pain. Included in the category of noncardiac conditions responsible for chest pain are many musculoskeletal affections of the thoracic cage, shoulder girdle, and cervical

and dorsal spine. Diseases involving the lungs, pleura, diaphragm, esophagus, the cervical plexus, and intercostal nerves may produce distress which simulates pain of cardiac origin. Referred pain of functional and organic diseases involving structures below the diaphragm may do likewise. It should be stressed that the diagnosis should be made by careful evaluation of the symptoms and not by exclusion of the innumerable conditions which may have some vague resemblance to the discomfort of true angina.

I have yet to find a better description of true angina than that given by White,[11] who states that in the majority of instances (90% of patients) angina presents no difficulty in diagnosis. My personal observation of his technique in eliciting the details of the symptomatology of coronary disease have been invaluable in my own training. Since objective findings of uncomplicated angina are nil except for those instances where transient or persistent abnormalities are found in the resting or exercise electrocardiogram, it is important to be very familiar with the clinical characteristics of other conditions which may simulate angina or modify the characteristics of angina if they coexist in the same patient. This means that the physician who assumes the responsibility of making a diagnosis of angina should be thoroughly familiar with the findings of the innumerable conditions which produce chest pain,[12-16] be they orthopedic, neurological, pulmonary, gastrointestinal, or functional, as well as the recognized variants of the anginal syndrome.[17] He must also appreciate that the patient with well-established coronary disease often develops an anxiety state which may be more symptomatic and disabling than the coronary disease itself. Likewise, spinal arthritis, bursitis, gallbladder disease, and hiatal hernias occur frequently in the same age group as those who have coronary disease, and they frequently occur together. For these reasons, a good internist, well-trained and experienced in cardiovascular diseases, is less likely to make a diagnosis of spurious coronary disease than the highly trained cardiologist whose training and experience today is often limited to the technical features of cardiovascular diseases.

In the initial evaluation and long-time follow-up of a large group of military personnel who were evaluated because of symptoms or findings suggesting coronary disease, it was found that when chest pain was the presenting symptom, the most frequent cause was an anxiety state which in many instances had been aggravated by previous management.[18,19] Cervical arthritis with associated radiculitis or radicular pain from other causes including ruptured cervical discs, bursitis, fibrositis, and various musculoskeletal disorders about the shoulder girdle were the most frequent organic conditions identified in those with normal cardiovascular systems. Gallbladder disease, peptic and esophageal ulcers, esophagitis, cardiospasm, hiatal hernias, and pancreatitis were less frequent but were often very troublesome in the differential diagnosis. These had often resulted in an erroneous diagnosis of coronary disease. The electrocardiographic changes after exercise were found useful in providing objective evidence of coronary insufficiency and in establishing a correct diagnosis in this large group of patients. In the use of this procedure, it is important that the test be properly performed and interpreted; otherwise its use only increases the incidence of spurious disease.[20,21]

Physicians frequently contribute to the spurious diagnosis of coronary disease by the misinterpretation of a laboratory test, especially the electrocardiogram.

The character of the findings in the resting electrocardiogram which have been found to contribute most frequently to spurious coronary disease by misinterpretation or over emphasis are (1) *ST*-segment and *T*-wave variations and abnormalities in these components associated with a host of electrolyte and metabolic abnormali-

ties or with the effects of drugs; (2) *QS* complexes in a limb or precordial lead associated with positional changes of the heart; (3) accelerated atrioventricular conduction with an electrocardiographic pattern of left axis deviation (Type B, WPW pattern of Sodi-Pollares[22]), which is erroneously interpreted as an infarction of the posterior wall of the left ventricle; (4) intraventricular conduction abnormalities, especially left bundle branch block and atrioventricular conduction disorders; (5) arrhythmias, especially those arising from a ventricular focus.

In my own experience I have found that the most frequent electrocardiographic changes which had contributed to a well-established spurious diagnosis was the overdiagnosis of coronary disease on the basis of nonspecific *T*-wave abnormalities, either in the resting electrocardiogram or the electrocardiogram after exercise. Such findings are common in persons with anxiety states and neuroses and frequently in young Negroes. On the other hand, the commonest organic cardiovascular conditions which resulted in electrocardiographic changes misdiagnosed as organic coronary disease were those associated with pericarditis, myocarditis, and pulmonary infarction and other causes of acute and chronic pulmonary hypertension. Occasionally, electrocardiographic changes associated with noncardiac conditions, such as myxedema and hyperthyroidism; the cardiovascular manifestations of pheochromocytomas, hypocalcemia, and nutritional disorders were misinterpreted as those of coronary disease.

The findings of myocardial insufficiency, cardiomegaly, and disorders of conduction or arrhythmias, singly or in combination without apparent cause in a patient over 40 years of age are often considered as clinical manifestations of occult or masked coronary disease, chiefly by a process of exclusion of other common etiological types of heart disease associated with these findings. This results in an erroneous diagnosis of coronary disease. The group of primary myocardial diseases,[23] or the so-called noncoronary cardiomyopathies[24] must be considered in the differential diagnosis in such patients. The error here is not too important in most instances, as the types of organic diseases that are presently included under these categories offer a poor prognosis and few have a specific therapy.

In recent years, the ballistocardiograph, which at this stage of its development should be used only as a research tool, has been used by some in the clinical evaluation of patients. When used in this manner, it has contributed its share to spurious diagnosis. When enzymal tests were shown to be helpful in the identification of myocardial necrosis after coronary occlusion, errors again occurred from overdiagnosis from improper use and interpretation of the results of this procedure. Many fail to appreciate that this test is nonspecific and that myocardial necrosis is just one of the numerous conditions which can increase enzymal activity. The laboratory finding of an elevated blood cholesterol or other abnormalities in blood lipids has been considered by some as sufficient to establish a diagnosis of coronary disease, especially if the person in whom these findings occur happens to have chest pain or an associated abnormality in the electrocardiogram regardless of the nonspecific character of these findings.

For some years the electrocardiogram and the chest roentgenogram have been a part of routine and periodic examinations of military personnel, especially in career personnel. Recently there has been a tendency to add one or more blood tests, such as the determination of serum cholesterol, total lipids, or lipoproteins, either as actual or potential parameters of coronary disease. Similar procedures are now common in many industrial health clinics or are used in health surveys, private clinics, etc., for the detection of coronary disease or as predictors of coronary disease.

During years of experience as a cardiac consultant in the military service I have

had occasion to evaluate many persons who were totally asymptomatic, active, highly motivated, and efficient until they were informed of the results of the findings of a routine examination (usually an electrocardiogram) which was reported to indicate coronary disease. Some were not disturbed by this finding and reluctantly went through the procedures of cardiac evaluation, hospitalization, etc., in resolving the problem. Many others developed anxiety states which were greatly aggravated by the repeated examinations, hospitalizations, indecision, and often conflicting opinions. Some unfortunately were retired with a primary diagnosis of coronary disease in this difficult process of evaluation. In others, it became difficult to obtain rehabilitation even after the diagnosis of coronary disease was well excluded, and they became ineffective and incapacitated by the cardiac neurosis. As previously stated, the iatrogenic heart disease which develops under such conditions usually takes root in a person with a preexisting inadequate personality. A similar finding has been reported by others. The finding of an abnormality or questionable abnormality in a health survey, periodic or annual examination, or research study involving laboratory tests requires the exercise of good professional and clinical judgment and proper explanation to the patient. Otherwise, one may unintentionally do harm to some person. The so-called "heart-scare" neurosis is more frequent and more incapacitating when it arises from a suspicion created by some finding which reportedly indicates coronary disease. One sees this daily from patient's reactions to a report of an abnormal cholesterol determination. When the diagnosis of coronary disease is made solely on the basis of an elevated cholesterol, I believe that it can be called spurious coronary disease. Others consider the finding of an elevated cholesterol or other abnormalities in blood lipids as definite precursors of coronary atherosclerosis. Where the statistical relationship between proneness toward coronary disease and certain critical variables has been studied, the findings indicate that such relationships apply only to groups of persons and not to an isolated finding in a given person.[25,26]

Summary

Factors which have been found to contribute to the origin of spurious coronary disease are (1) the subtle nature and protean manifestations of organic coronary disease which makes diagnosis difficult, (2) the neurotic disposition of the patient, and (3) the attitude and action of the attending or consulting physician.

Reports of basic research and clinical investigative studies dealing with the etiology, diagnosis, and therapy of such an important and feared disease as coronary disease should be presented to the medical profession and the public in such a manner as to avoid undue anxiety, a potent factor in the cause of any spurious disease.

The patient most often contributes to the development of spurious diseases by possessing a personality defect. Prevention or eradication of this defect is difficult, as it is either inbred or dependent upon years of faulty adjustments.

The physician contributes chiefly by his failure to recognize the neurotic nature of the patient and the existence of a state of anxiety. Often when these two conditions are recognized in a patient, the physician contributes by his attitude toward the patient's neurotic or anxiety symptoms or in their management. Less frequently he initiates spurious disease by his actions in the hurried pronouncement of a diagnosis of coronary disease, based on misinterpretation of symptoms, physical findings, or nonspecific laboratory tests, either in a patient with an anxiety state alone or in one with anxiety plus less serious organic disease. Such errors in diagnosis, again, are most likely to produce disabling spurious coronary disease in persons possessing a personality defect.

Periodic and recurring examinations and screening studies are helpful in the detec-

tion of asymptomatic coronary disease. The use of "normals" are necessary in the evaluation of tests or as potential parameters of coronary disease. These studies should be performed with caution and after thorough orientation of the subject. The finding of an "abnormality" or questionable abnormality should be carefully evaluated before it is presented to the patient or therapeutic or preventive measures are instituted. Heart scare and spurious coronary disease are undesirable and preventable complications of our national efforts in the study and treatment of this disease. Every precaution should be taken to avoid or minimize these complications.

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Diet and Coronary Heart Disease

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The most pressing medical problem of the Western World is that of coronary heart disease. The past 15 years have seen a revolution in attitude toward this problem. The old pessimistic view that atherosclerosis is inevitable and immutable has given way to an optimism that atherosclerosis can be reduced to its chemical parts, can be known, and, in time, prevented. These new opinions are suspended upon a tenuous network of hypotheses that sway and tear in the face of criticism, prejudice, and windy debate. Nevertheless, the hypotheses are useful and indispensable parts of the scientific method, and they deserve careful tending. Chief among them is a belief that diet is important to the pathogenesis of atherosclerotic disease.

It would be vain to suppose that man is so ingenious that he would never devise some piece of progress which would backbite him. It is worth considering that a way of life may have been created which includes, in one way or many of its attributes, the agents responsible for atherosclerosis. In a narrower sense, a kind of dietary or way of feeding which is harmful to health may have been created. The most interesting and popular hypothesis now considered states that an epidemic of atherosclerotic disease has been created by an inadvertent "progress" in the Western diet. It should not be assumed that an epidemic has, in fact, been demonstrated. The evidence for this has been considered in another place.[1] There can be no reasonable doubt that coronary heart disease (CHD)* is a prevalent disorder. It is a particularly important problem of epidemiology to determine whether the force of the morbidogenic agents have changed, because such evidence might serve to identify a prevention. The characterization of these changes is a complicated and unsolved problem involving, as it does, changing concepts of the disease as well as changing diagnosis, interest, and medical facilities. Physicians should reflect on how they would have diagnosed and signed out a man of 50 who died suddenly 25 years ago.

The belief that CHD has increased leads to the necessity for the most careful examination of what the Western diet is, how it has been changed, and how it can be shown to relate to atherogenesis. It is not necessary in this consideration to pass on the practicality of altering dietary habits. The need is only to understand relationships. The obstinacy of people in accepting and acting on the dangers of the smoking fad must emphasize that the learning of mechanisms and the implementation of preventions are two very different problems.

There are six hypothetical causative agents which are presently considered in

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* It is now fashionable to call the old disease by a new term, ischemic heart disease. This name has been adopted by the WHO Special Committee on Atherosclerosis. The new name would be somewhat more acceptable if its proponents could agree on how to spell it. Nor is it likely that physicians and patients will soon be accustomed to refer to their "ischemics."

SIX HYPOTHETICAL CAUSES OF CORONARY DISEASE

1. HIGH FAT INTAKE
2. UNSATURATED FATTY ACID DEFICIENCY
3. HIGH CHOLESTEROL INTAKE
4. VITAMIN B_6 DEFICIENCY
5. OBESITY
   a) Overeating
   b) Underactive
6. NERVOUS STRAIN

Figure 1

atherosclerotic disease (Fig. 1). Five of these are directly involved with diet. The sixth, nervous strain, is scarcely in the realm of science because it has defied either definition or measurement. It is well to remember, in the first place, that a consideration of human diet is seriously limited by the inability to measure this. The human diet changes according to person; religious training; social, marital, and economic status; the season; the day of the week, and the stage of life. Because of its variety, the American diet is susceptible to no more than a general kind of description. In a general way, the simpler and more monotonous the diet the easier it will be to measure. The difficulty of measuring existing dietary habits must be exaggerated when estimates of the diets of 50 or even 10 years ago are made. It was inevitable that these complexities would attract successive crops of "simplified explanations" of the relationship of diet to heart disease.

The hypothesis that excessive levels of dietary fat have caused, or at least contributed to, the development of atherosclerotic disease is particularly the work of Ancel Keys. Beginning in 1950,[2] Keys and his colleagues have vociferously pressed the proposition that the rise of CHD is a consequence of excessive fat in the diet. It has been his belief that not the quality but the quantity was important. This concept originally displaced, indeed disposed of, the older and more debated than studied concept that excessive dietary cholesterol was the causal agent. The involvement of cholesterol goes back many decades to the demonstration that rabbits, when fed cholesterol, would develop a disease like human atherosclerosis. For many years these observations, although amply confirmed, were little known and considered in human problems. A few pioneers, Leary,[3] Hueper,[4] and Page[5] reminded clinicians and scientists that cholesterol intake might be important, but these warnings were ignored or scoffed at with either indifference (the clinical problem was not then very conspicuous) or written off as an exotic laboratory demonstration without relevance to human disease. The concept that some level of exogenous cholesterol may produce hypercholesterolemia and atherosclerosis through a kind of metabolic decompensation has received dramatic support from the experimentation of Taylor et al. at Presbyterian-St. Luke's Hospital in Chicago.[6] These workers have produced significant hypercholesterolemia in rhesus monkeys by feeding butter to supply 42% of the calories. Feeding an equivalent amount of margarine, free of cholesterol, did not produce the effect. They have described a myocardial infarction in a monkey which simulates the human disease in all respects, and this is, to my knowledge, the first such demonstration. It seems clear that exogenous cholesterol is still a factor in the research problem. The central position of cholesterol as a suspected agent in causations may have been prematurely abandoned. Keys changed this. With a minimum of evidence, he discounted the role of cholesterol because he could not raise the serum cholesterol levels of 14 men fed 1 gm. of supplementary crystalline cholesterol per day for 28 days.[7,8] It seemed reasonable to him that these short trials were in fact decisive for a disease that requires 30 to 50 years for its usual life history. Keys replaced the idea of the stigma of cholesterol with an indictment of the total dietary fat. Two kinds of evidence were used. In the first place, the group at Minnesota, as well as others, confirmed the observations of Starke,[9] and Hatch et al.[10] to the effect that reducing the dietary fat would lower the

serum cholesterol level. It was not always emphasized that individual differences in the response were great (some subjects did not respond with a lower cholesterol level in the serum—rather, it rose!). For example, of the 44 patients studied by Hatch,[10] 5 showed a rise of serum cholesterol and 8 of the other 39 showed a fall of 10 mg. % or less. These were patients studied on a metabolic ward when shifted from a house diet with 85 gm. of fat per day to a rice diet with 3 gm. of fat per day. Hatch concluded, "The response of the serum lipids and lipoproteins to restriction of dietary fat was not predictable for any given patient." The other support for Keys' hypothesis came from an assortment of global observations of different cultural groups using especially estimates of dietary fat and prevalence of CHD. This kind of activity had been predicted and advocated many years earlier by Dr. Paul White, who wrote in 1938[11]: "We cannot experiment on man and we cannot always apply animal experiments to man. But we can make use of the many experiments that nature herself is constantly making on man. . . . How may this study be carried out? . . . it might still be the private endeavor of a group of individuals or of a single well-to-do enthusiast who is burning with the desire to be a pioneer in this vital work." The enthusiast Dr. White found in Ancel Keys. The heat has been notable! Out of his eclectic, cross-cultural samples, Keys constructed what some have come to call the Keysian curve. This is a graphical relationship of fat intake expressed as per cent of fat calories and death rates assigned to CHD (Fig. 2). This relationship had a wide publicity in both the scientific and lay press and has, no doubt, influenced the diets of large numbers of people. There was the uncomfortable fact, for scientists at least, that no mechanism for this relationship of dietary fat was proposed, nor was there much effort apparent to demonstrate one. The energy was spent in the exercise that, since observations A and B coincided, A must cause B. The treatment was obvious. Another deficit was the difficulty of demonstrating that adding fat to a human dietary would lead to a measurable increase of serum cholesterol level. This would seem

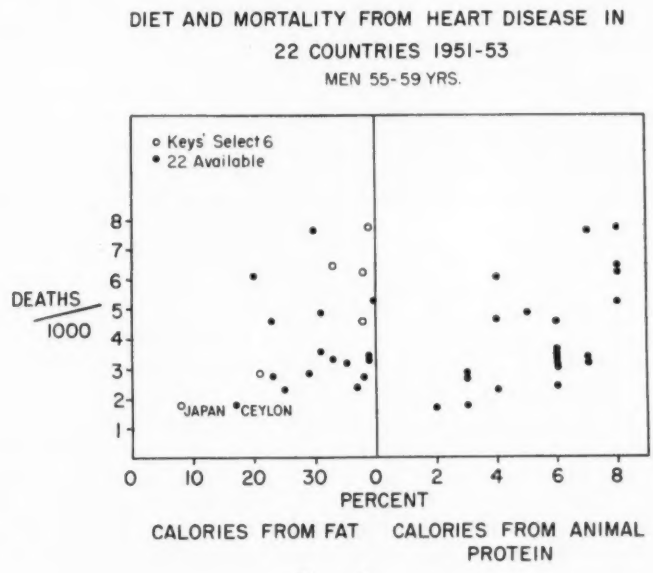

Figure 2

to have been the direct approach. The most substantial support for the hypothetical role of dietary fat in contributing to hypercholesterolemia has come from laboratory trials with human subjects kept on fat-restricted regimens. An especially lucid and interpretable study is that of Horlick.[12] When young adults were placed on a low-fat diet, the serum cholesterol level fell. This is the available and commonly used index of atherogenesis. When fats were added, the cholesterol level remained low but went no lower with corn oil which is an unsaturated oil. The serum level of cholesterol also remained low when hydrogenated vegetable oil was added, but since these materials caused gross steatorrhea, it is plain that the trial was invalidated. This is one of many demonstrations that lowering the total fat intake—and this is exceptionally high among Americans—will often lower the serum cholesterol level. We must assume that such an effect is worthwhile, and we make this assumption in the belief that hypercholesterolemia is somehow productive of atheroma. These facts are the basis of the dietary fat hypotheses in relation to atherosclerotic disease.

Two crushing blows came to this hypothesis. In the first place, two professional epidemiologists[13] demonstrated that the Keysian curve disappeared in a meaningless welter of points when not a select 6 but all 22 of the available Food and Agricultural Organization national data were considered (Fig. 2). The other attack was a competing hypothesis.

In 1952 Te Groen et al.,[14] in Holland, published evidence that the kind of fat affected the serum cholesterol level. When vegetable fat was fed, the level dropped; when dairy fat was fed, the level rose. This work was not widely known. Subsequently, Hatch[10] found that the low-fat rice diet would often depress the serum cholesterol level. Kinsell,[15] Ahrens,[16] and Bronte-Stewart[17] had observed a depression of serum cholesterol level with vegetable fat. A fierce contention then arose over the merits of the unsaturated fat hypothesis vs. the total fat hypothesis. For no better reason than its youth and vigor, the unsaturated fatty acid hypothesis now prevails. It has several weaknesses. In the first place, this, as all hypotheses of atherogenesis, must use an indirect index of the anatomical process; it is difficult, if not impossible, to accurately measure this association. While the association between serum cholesterol level and atherogenesis is good in experimental animals, it is much less well-known in human beings. In the second place, all these dietary relationships, and especially that of short-term treatments with the level of serum cholesterol as the index, are limited by the biological variability of these levels.

If the level of cholesterol is measured sequentially in human subjects or in experimental animals kept in stable and protected environments, it is found to vary. This variation, as Watkin[18] has shown, is comprised of two measurable parts which may be called technical variation, meaning that contributed by methodological variations and biological variations. In an analysis of variance, the total variance. (S_T), less the technical error (T_E), is the biological variation (S_B). A considerable confusion has been contributed by the failure to recognize that these variations will tend to obscure and confuse therapeutic trials. It must be clear that one cannot evaluate therapy unless preliminary estimates of the subject's variability is done. It should also be appreciated that the technical error (T_E) will vary with the cholesterol level. Since it appears hopelessly true and invariate that clinical investigators will use the most improbable and least useful subjects for trials, that is, those with either very high cholesterol levels (who "need something done") or those with very low cholesterol levels (who are "those handy medical students and house men"), it is especially important that the variability of the high levels or the invariability of the low levels should be measured. Rivin et al.[19] have concluded that, with their method for cholesterol which had a T_E of 27 mg. %, it would be

necessary to find a change of 60 mg. % before an effect had been demonstrated. This is an excessively high T_E and, as it is usual to measure serially the meaning of a smaller change, will often be decisive. Nevertheless, it must be clear that many conclusions about effectiveness have been based on trivial statistical manipulations of inadequate data.

In this connection, it may be appropriate to suggest the necessity for demonstrating that a laboratory can, in fact, measure cholesterol creditably. If the laboratory is given divided specimens over a few weeks or a month, in such a manner that they cannot identify pairs, one can calculate, after 20 or 30 such pairs, the equation given in Figure 3.

$$T_E = \sqrt{\frac{\text{SUM DIFF.}^2}{2 \times \text{PAIRS}}}$$

FOR CHOLESTEROL T_E SHOULD BE $\leq$ 5 MG.%

Figure 3

This should be less than 5 mg. % in a competent laboratory. If it is higher, there is trouble, and the proper place to do research is not with patients or with therapeutic trials but with methods. It does not matter so much which method is used so long as it performs satisfactorily. With a suitable low T_E, the other necessity is that of establishing the method's relationship to other methods in terms of authenticity. This is of less importance in sequential studies of effects of therapy.

The magnitude of the effects of the unsaturated fatty acid treatments are variable, but they occur, and the effect is real. The mechanism is unknown and there have been few suggestions. As with the total fat hypothesis, more energy is spent in sustaining the hypothesis than in understanding it. It has not been finally established whether the effectiveness of vegetable oils (such as corn oil) in lowering the level of serum cholesterol is caused by a specific chemical effect of its unsaturated fatty acids or whether the effect is instead a replacement of other materials, e.g., saturated fatty acids which are positive causes of hypocholesterolemia. Horlick [12] has shown in human subjects that the addition of corn oil to low fat diets which had already reduced the serum level of cholesterol would not further depress the cholesterol level. These data and others like them suggest that corn oil acts in a substitutive or neutral way, replacing some noxious and presently unidentified material. It is very clear that simply adding a few tablespoons of vegetable oil to the usual diet will accomplish nothing.[20] This will disillusion the easy dieters. It must also be apparent that the American diet is, and has been for several decades, abundant in the vegetable oils, and these are the rich sources of unsaturated fatty acid. Vegetable oils, corn, cotton, and peanut oils are rich in the so-called essential fatty acids. It is inconceivable that Americans could develop unsaturated fatty acid deficiency. The contention of Sinclair [21] that this deficiency is a relative matter, a disproportion of saturated and unsaturated fatty acids, is difficult to answer, but it is significant that no direct feeding experiments have demonstrated the relationship. There are two interesting, if remote, possible explanations of the action of unsaturated fatty acids on the serum cholesterol level. The effects could be mediated through an induced loss of sterols via the bowel, a kind of steatorrhea induced by unsaturated fatty acids and not so by saturated fatty acids. If this were true, the vast preoccupation with unsaturated fatty acids would become the greatest unpremeditated study of cathartics and laxation ever undertaken! Another possibility that has not been eliminated is that hydrogenation of fat may introduce some noxious substance. This deserves careful examination because the time relationships of the apparent rise of CHD and the commercial production of hydrogenated fats are suggestively similar.

The present evidence does not support the clinical application of unsaturated fatty

acids (either as such or as proprietary drugs) as a preventive or therapeutic tool. It would be well for clinicians to distinguish between the research and clinical aspects of the atherosclerosis problem. At the present time there is an active research attack; there is no prevention or cure. The exploitation of fragmentary and indecisive research findings is premature.

It is useful to consider the pathogenesis of clinical events according to the scheme shown in Figure 4. The demonstrable and

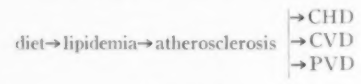

Figure 4

conspicuous events in this system are the serum cholesterol levels and the clinical events. Since there is no way of detecting the anatomical lesions in life, it has become common to assume that measurements of cholesterol and mortality from CHD are, in fact, representations of the extent and progress of the atherosclerotic lesion in the vessel wall. Pathologists are well aware of the inconsistency here, for they see many persons dead of CHD with minimal atherosclerosis, and conversely, many with atherosclerosis who died late of other causes. It should be considered that the pathogenesis of the events which precipitate the clinical event may be independent of those which produce the mural lesion. The two processes may be related only in the sense that they coincide.

The diet is involved in consideration of the precipitation of the clinical events because the blood fats seem to effect blood coagulation and the diet influences the blood fats. It has been suggested that an increase of blood lipids increases the coagulability of blood.[22] Here was a mechanism for reinforcing the damaging role of dietary and blood lipids in CHD. The difficulty is a familiar one. The methods for measuring coagulability are undependable. This is the most likely explanation for the profound disagreements among investigators. Waldron et al.[23] reported that lipemia increased the tendency of blood to coagulate. This observation was not always confirmed.[24,25] It now appears demonstrated that a large fat meal—and this is 50 to 120 gm. of butter fat amounting to 500 to 1,000 calories—will produce an increase in the coagulability of blood when this is measured in nonwettable tubes. The effects on prothrombin time are smaller and less definitive.[26] It remains to be shown that the incidence of coronary occlusion is localized during the three- to five-hour period after large meals when this in vitro coagulation change has been demonstrated. It has been shown by Robinson and Poole[27] that the effective component of the lipemic sera is not the neutral fat, but a specific kind of phospholipid called ethanolamine phosphatide. At the present time, the short-term effect of diet in precipitating CHD is no better established than the debatable long-term effect of diet in influencing atherogenesis. In passing, it is of interest that the demonstration of effect of a meal on coagulation required a very large meal. It may be appropriate to examine the relationship of diurnal distribution of calories. The working man's three square meals were surely a more equal distribution of intake than the executive's citrus-and-toast breakfast, salad lunch, and steak-and-potatoes dinner. This kind of contemporary dining may be important to the problem.

It is clear that the extensive laboratory research program has not produced a definite and dependable course of action for the prevention or reversal of atherosclerotic disease. There is an alternative source of useful information. This is the experience and observation obtained from the associations of the disease. Every physician knows something of the life history of CHD from his observation of patients with it. There are, in addition, the data of several epidemiological surveillance studies among which the Framingham Study of the National Heart Institute is prominent. This study is now 10 years old, and a preliminary description of the experience with CHD has been pub-

INCIDENCE OF ASHD IN FOUR YEARS AMONG MEN

AGE 45 - 62 YEARS

FRAMINGHAM HEART STUDY

Clinical Status			Number at Risk	New Disease	Rate/1000
All persons			877	51	58
Blood Pressure	Relative Weight	Serum Cholesterol			
High on two or more			105	15	143
High on one only			290	23	79
Borderline or medium on two or more			186	7	38
Borderline or medium on one only			198	5	25
Normal or low on all			98	1	10

Figure 5

lished.[28] The association of clinical attributes with the development of CHD in that population lead to the indictment of three characteristics: high blood pressure, obesity, and our old protagonist, hypercholesterolemia.

The relation of these three attributes to the observed incidence of CHD over a four-year period, in 877 men previously found free of stigmata of CHD, is shown in Figure 5. The three attributes contribute singly and they also show a cumulative effect, so that with all three present in large degree, 17 men showed the appalling probability of 5 to 12 to lose with CHD in a four-year period. This prediction belongs in the exclusive circle of near certainty in medicine. Each of these three attributes is subject to some control. Blood pressure can usually be controlled with drugs and careful attention to diet and electrolyte metabolism. Obesity can be prevented, or even reversed with this motivation, by attention to the balance between dietary intake and caloric expenditure. It should be appreciated that no "diet" or "plan" will accomplish this, but rather a systematic and permanent control of the two variables is necessary. Men will do this in the face of such a threat. The polemic concerned with the adequacy of proof of the effectiveness of weight loss in lessening CHD risk need not concern us. The data from life insurance sources is strongly suggestive. The complaints with this kind of data arise largely from those who would like to demonstrate that some pet thesis, such as total dietary fat, is the entire explanation. Weight reduction will also facilitate the lowering of blood pressure and serum cholesterol levels.[29] The serum cholesterol levels will be lowered by moderation of the total fat intake. The intake of fat among 402 men in the Framingham Study was found to be huge (mean, 157 gm/day; range, 57-299 gm/day) (Fig. 6).[30] A lowered intake of this con-

MEAN DIETARY INTAKES - AMERICANS 1957-58

FRAMINGHAM HEART STUDY

	N	Calories	Protein g.	Fat g.	Cholesterol mg.
Men	189	3346 ±750	122 ±24	157 ±39	729 ±217
Women	213	2268 ±600	86 ±20	110 ±34	508 ±171

Figure 6

centrated caloric source will also facilitate weight reduction, although the prevalent belief that a low-fat diet is a low-calorie diet, and thus reducing, is obviously false. People, like pigs, can fatten on carbohydrates.

A reasonable summary of an action program at this stage of our knowledge could be itemized in six recommendations as follows:

To the clinician:

1. Diagnose and report disease, and especially cardiovascular disease, with all the accuracy you can command. These reports are a powerful aid in understanding and controlling CHD.

2. Beware of faddists, and especially the academic faddists who, under the guise of science, advise your patients in the press and sometimes advise you on how to prevent and cure CHD. They are selling short.

3. Distinguish between research procedures and therapeutic procedures. You do your patients a disservice in applying each vague and fragmentary rumor of a treatment that leaks out of a research laboratory and too often shows up in a slick paper advertisement.

DRUGS - DIETS - DOUBTS

1. GET THIN - KEEP THIN
2. MODERATE FAT INTAKE
3. EXERCISE REGULARLY

EXPERIMENTAL	SPECIAL R_x
1. NICOTINIC ACID	1. ESTROGENS
2. SITOSTEROL	2. THYROID HORMONE
3. "Mer 29"	3. CHOLESTEROL RESTRICTION

IGNORE

1. LIPOTROPICS
2. PYRIDOXINE
3. UNSATURATED FATTY ACIDS

Figure 7

To the laboratory scientists:

4. Learn how to measure the attributes you use. Learn to live within your intellectual income.

5. Avoid the sawdust trail in defense of a shaky hypothesis. Problems are solved by experiment—not by debate.

To the laity:

6. Keep thin; exercise regularly and actively; eat moderately, especially with respect to fat. What is "moderately"? Avoid gravies, dressings, spreads, and deep-fried foods as well as the fatty desserts. Further than this it is not safe for me to go!

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Evaluation of Abnormal Stature in the Adolescent and Young Adult

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Stature is perhaps the simplest physical dimension of man to measure, yet the physiological processes involved in its attainment are among the most complex and poorly understood. This state of affairs can be ignored by the physician until he is confronted with a person who has failed to achieve satisfactory height or who has grown excessively tall. The physician then must decide if indeed an abnormality exists and, if so, what is its basis. The report that follows is concerned with the methods of investigation, results obtained, and diagnoses made in the study of such persons during the past four years.

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Subjects

Patients whose cases are contained in this report were adolescents or adults in whom abnormality of stature was either the chief complaint or a significant feature of the patient's illness, with one exception. Nine had abnormally short stature, or dwarfism; this group included 4 men and 5 women, ranging in age from 18 11/12 years

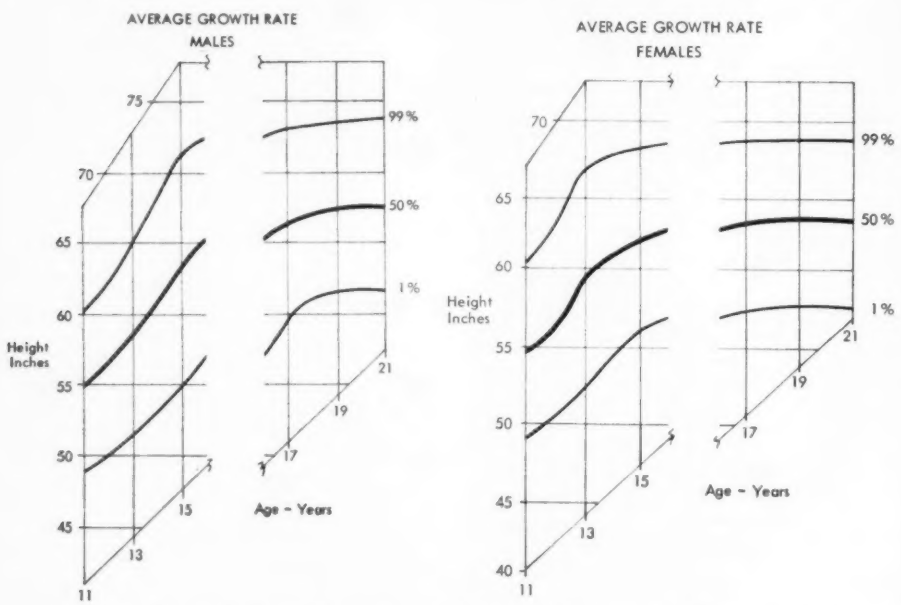

Fig. 1.—Height charts modified from Burgess. The charts are schematically broken at age 16, the dividing age between the Pediatric and Medical Services at the University of Missouri Medical Center. The heavy lines indicate the average growth curves for American males and females; the lighter lines above and below indicate the 99 and 1 percentile points for each age. The curves are based on data collected before 1937.

TABLE 1.—*Dwarfism Data*

Patient	Date	Age, Yr.	Ht.	Hand-Wrist Bone Age, Yr.	Mental Age	24 Hour Urine 17-OHC (Mg/24 Hr.) 17-KS (Mg/24 Hr.) FSH (r.u/24 Hr.)	Thyroid Function	Lateral Film of Skull	Sulfation Factor	Diagnosis
1	9/55	18 11/12	5′ ¼″	15	N	—	N	N	—	Delayed adolescence, familial shortness
2	9/58	22 9/12	4′1″	Adult	? N	2-3 2-6 0	N	Marked craniofacial malformation	1.07 *	Primordial dwarfism
3	11/58	App. 28	4′5 ¼″	Adult	Sub N	1-2 5-8 22	N	N	0.91 *	Gonadal aplasia, primordial dwarfism
4	4/59	51	5′0″	Adult	Sub N	3-4 6-7 0	Low BMR	N	—	Myotonia dystrophica, primordial dwarfism
5	5/58	21 6/12	4′6 ½″	16	N	4-5 ? 11.8	Sl. D	Suprasellar tumor	—	Pituitary dwarfism, craniopharyngioma
6	4/56	22 9/12	4′1″	5	Sub N	—	Severely D	N	1.43 *	Cretinism
7	4/59	19	4′ ½″	Adult	N	—	—	N	—	Achondroplasia
8	1/59	52	4′0″	Adult	N	11.5 9.6 —	N	N	—	Eccentro-osteochondrodysplasia
9	4/57	17 7/12	4′6″	15	N	4-5 11.8 0	N	N	—	Diabetic pseudodwarfism

* Within normal limits. *N* indicates normal; *D*, decreased.

to 52 years; with two exceptions all were under 30. Two patients, a man, age 22 and a woman, age 38, presented with excessive height.

Methods

As a guide to "normalcy" of a patient's height, use was made of the height charts prepared by Burgess.[1] These, in a modified form, are presented in Figure 1. The years from 11 to 21 are included, broken schematically at age 16, the arbitrary age of division between the pediatric and medical services at the University of Missouri Medical Center. These charts show, in addition to the mean age of the American females and males, the 99 and 1 percentile levels, thus affording an indication of degree of deviation. Height, span, and lower segment (from the top of the symphysis pubis to the floor) were measured; the upper segment (symphysis pubis to vertex) was obtained by subtraction, and the relative dimensions of the two segments were expressed in the standard upper segment/lower segment ratio. Certain details of history were most carefully pursued: size at birth of patient, his mental and physical development in childhood and puberty, sexual development in late adolescence or adulthood, and familial history relative to stature, rate of development, mental deficiency, and skeletal abnormalities.

Mental age was estimated when indicated, with use of the Stanford-Binet and Wechsler-Bellevue tests.

To determine bone age, an x-ray in the AP projection of both hands and both wrists was obtained. Usually this could be accomplished with a single 8×10 in. film.

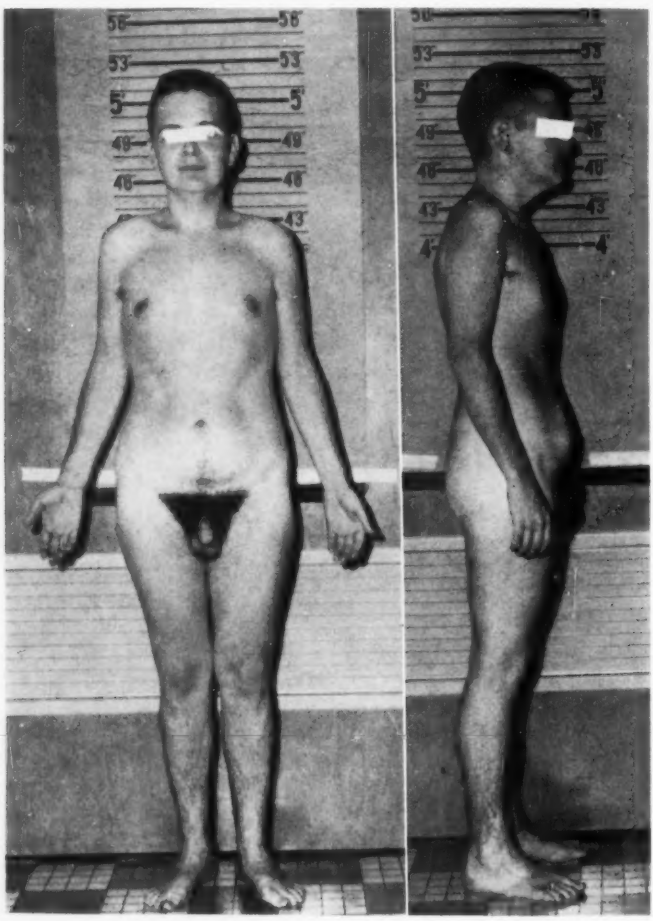

Fig. 2*A* (Patient 1).—Age 18 11/12 years. Heredofamilial short stature and delayed adolescence. Measured height, September, 1955, was 5′¼″.

Fig. 2*B* (Patient 1).—Radial and ulnar epiphyses open. Bone age, approximately 15 years. September, 1955.

In evaluation of the endocrine system, the following procedures were used. Anterior pituitary gonadotropin activity was assayed in one or more 24- or 48-hour urine samples with use of the method of Albert.[2] In a few instances, an indication of growth hormone activity was obtained by measurement of the serum sulfation factor * which has been shown to correlate well with growth hormone activity.[3] Thyroid function was assessed with use of the standard methods of serum total cholesterol, protein-bound iodine, radioactive iodine uptake, and, in some instances, the responsiveness of the thyroid to stimulation by thyrotropic hormone. Adrenal cortical function was determined by measurement of total 17-hydroxycorticoids and the neutral 17-ketosteroids in each of three 24-hour urine collections, with use of the methods of Porter and Silber[4] and a modification of the method of Drekter,[5] respectively. To evaluate sexual development and gonadal function, several procedures were employed. Smears from the buccal mucosa were obtained and examined to determine chromatin pattern. With the method used, smears from

TABLE 2.—*Excessive Stature Data*

Patient	Date	Age, Yr.	Ht.	Hand-Wrist Bone Age, Yr.	Mental Age	24 Hour Urine 17-OHC (Mg/24 Hr.) 17-KS (Mg/24 Hr.) FSH (r.u/24 Hr.)	Thyroid Function	Lateral Film of Skull	Sulfation Factor	Diagnosis
10	10/58	23 2/12	6'4"	17	N	— — 3.3	D	Enlargement of sella turcica	1.03 *	Gigantism, acromegaly, and hypogonadism
11	12/58	38	6'2"	Adult	Sub N	4.0 — —	N	N	—	Marfan's syndrome

* Within normal limits. *N* indicates normal; *D*, decreased.

* Serum sulfation factor determinations were performed by Dr. William Daughaday, Washington University School of Medicine, St. Louis.

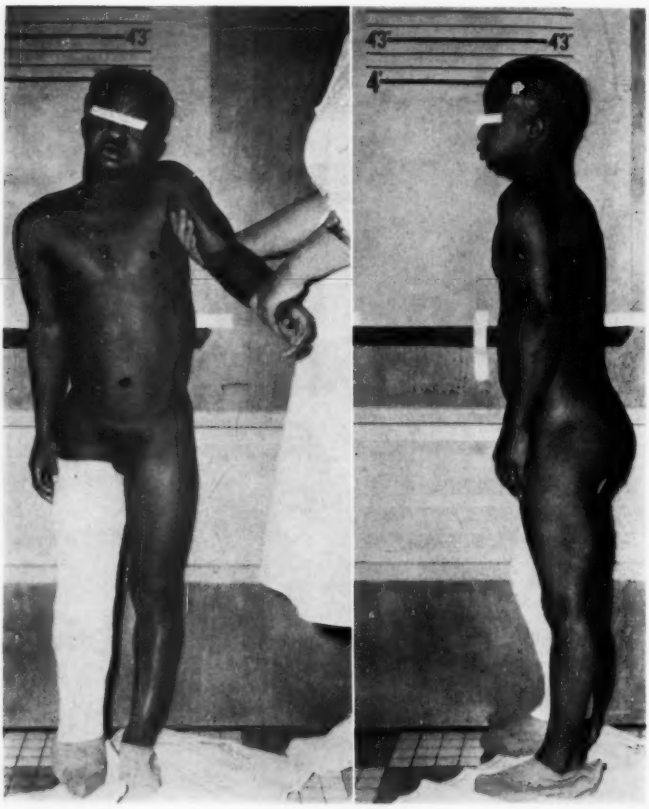

Fig. 3A (Patient 2).—Age 22 9/12 years. Primordial dwarfism with cranium bifidum occulta and craniofacial dysostosis. Measured height, September, 1958, 4'1".

normal females had 50% or more of cells containing female chromatin; in smears from normal males, 0% to 3% cells had a female chromatin pattern.† Seminal fluid examination and testicular biopsy were performed when indicated.

In addition to the above procedures, a single lateral x-ray of the skull was obtained in all patients. Depending on the problem presented, additional x-ray and laboratory studies and other procedures were obtained in several instances.

Results

Pertinent laboratory and x-ray data and the diagnoses made are contained in Tables 1 and 2. Full-view photographs of each subject and a reproduction of the hand-wrist x-ray are presented in Figures 2A through 12B. A brief abstract of each case follows.

PATIENT 1 (Figs. 2A and 2B).—An 18 11/12-year-old white male college student was referred because of "failure to grow normally" and obesity. Past history revealed normal birth, but growth was retarded from early childhood. Patient was treated with male hormone and thyroid at age 15; genitalia developed during 15th year, and he grew 2½ inches; thereafter, he grew but ½ in. Voice change had commenced but was incomplete; patient had commenced shaving once per week. Scholastically, the patient was superior. Mother, 5'6"; father, 5'7"; one brother, 6'0"; paternal uncle, 5'4", with one son, 5'2". Physical examination, height 5'¼", weight 141, moderate truncal obesity, little facial hair, female escutcheon; external genitalia normal except for decrease in size of right testis. Testicular biopsy revealed some decrease in spermatogenesis but was otherwise normal.

† The buccal smears were prepared and interpreted by Dr. Joseph Flynn, Department of Pathology, University of Missouri; the stain used with cresyl-echt-violet acetate, obtained from the Coleman and Bell Division of the Olin Mathison Company.

Fig. 3*B* (Patient 2).—All epiphyses closed. Bone age, adult. September, 1958.

Comment.—This patient apparently did not commence pubescence until after age 15 and still had not completed sexual and bone-age maturation by age 18 11/12 years; growth in stature appeared to have plateaued. The role of the hormone treatment is problematical. The clinical picture of delayed adolescence has been clarified by Wilkins,[6] who points out that the patient usually has been smaller than his peers in childhood; however, this difference becomes greatly magnified when the patient's contemporaries commence the pubescent growth spurt and begin to develop sexually. There ensues a period of three or more years during which the patient's failure to develop is increasingly conspicuous. When his growth spurt does occur an average height is obtained in some but not all instances.

PATIENT 2 (Figs. 3*A* and 3*B*).—A 22 11/12-year-old Negro man was admitted with history of a fracture of the right tibia and fibula of four months' duration and dwarfism. He had been small since birth. Family history was negative for dwarfism. Patient had had no formal education but was of average intelligence; he was employed as a farm laborer. He denied any impairment in potentia. The fracture of the leg occurred during the course of a friendly scuffle with his brother. Physical examination, height 4 ft. 1 in. The patient's appearance was that of a well-developed but diminutive adult. There was balding, frontal bossing, shortening of the mandible, and beaking of the nose, giving the impression of premature aging. External genitalia were small. Studies of the patient's calcium metabolism revealed no abnormalities. Testicular biopsy revealed vacuolated Sertoli cells, greatly decreased spermatogenesis, and normal-appearing Leydig cells. Radiographic examination of the bony structures of the face and head revealed multiple deformities including a large cranial defect in the frontal bone, markedly underdeveloped mandible, and poorly formed teeth with blunted roots.

Comment.—This patient had multiple malformations in addition to dwarfism. The radiographic diagnoses were cranium bifidum occulta and craniofacial dysostosis. The latter is commonly associated with primordial dwarfism. Dwarfism has been reported to accompany cranium bifidum occulta.[7,8] The facial appearance of this patient suggested progeria, although the remainder of his physiognomy did not.

PATIENT 3 (Figs. 4*A* and 4*B*).—A (?) 28-year-old Negro woman, mentally retarded, was referred because of 4+ glycosuria and high blood pressure. No reliable past history could be obtained. On physical examination, height was 4 ft. 5½ in.; blood pressure, 180/120. The patient had a dull expression; the carrying angle was exaggerated; axillary and pubic hair were present; the vaginal introitus admitted one finger; the cervix and uterus were very small. The ovaries could not be felt. Smears of the vaginal mucosa revealed no estrogen effect. Smears of the buccal mucosa revealed a male chromatin pattern.

Comment.—A moderate degree of dwarfism is a common feature of Turner's

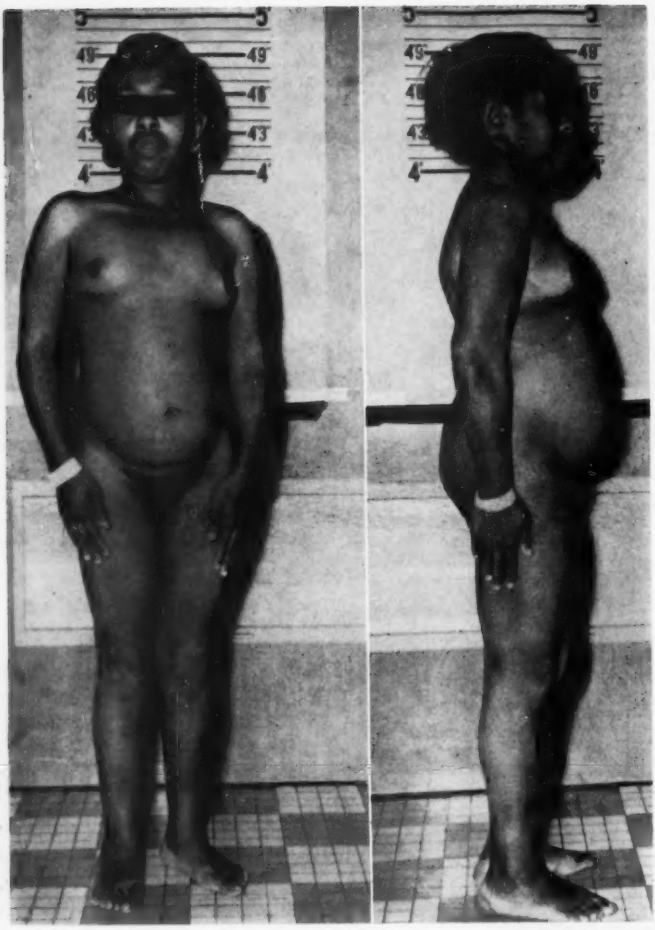

Fig. 4*A* (Patient 3).—Age c. 28 years. Primordial dwarfism associated with gonadal aplasia (Turner's syndrome). Measured height, November, 1958, 4'5¼". Chromatin pattern was that of a male.

Fig. 4*B* (Patient 3).—All epiphyses closed. Bone age, adult. November, 1958.

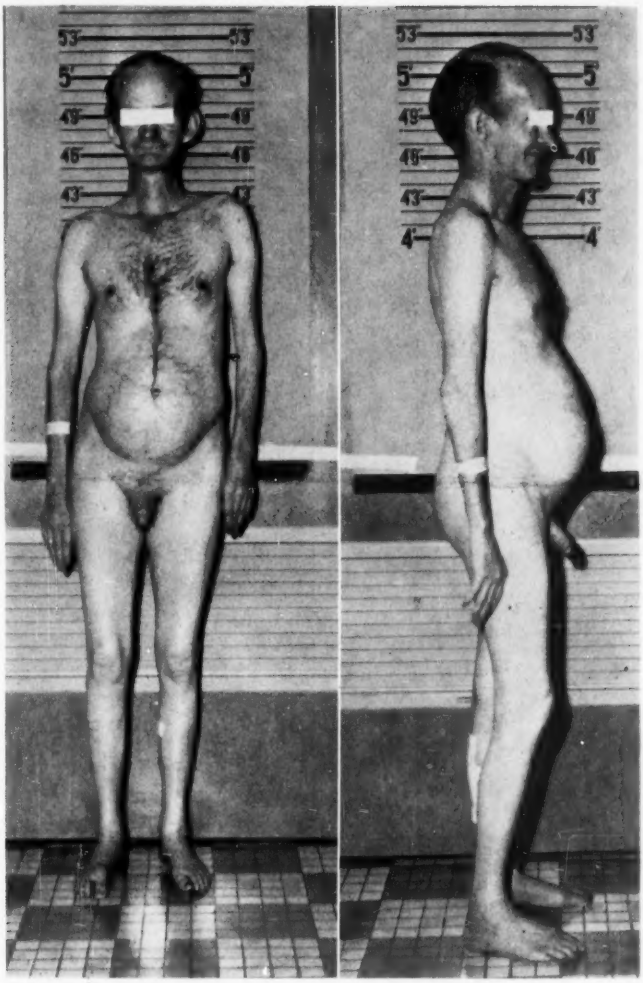

Fig. 5*A* (Patient 4).—Age 51 years. Primordial dwarfism associated with myotonia dystrophica. Measured height, April, 1959, 5'0".

syndrome, occurring as an associated malformation rather than as a consequence of gonadal aplasia. In the past, Turner's syndrome has been called ovarian agenesis. It now appears to be one of several disorders in which gonadal dysgenesis is an important feature. Genetic maleness, present in Patient 3, has been noted in about half of patients with this syndrome. Hypertension in this patient was not due to coarctation of the aorta. Diabetes mellitus appeared to be an unrelated finding.

PATIENT 4 (Figs. 5*A* and 5*B*).—A 51-year-old white single man was referred for evaluation of possible hypopituitarism. His chief complaint was progressive weakness of the legs of about six years' duration. The patient had been small for as long as he could remember; his height and weight in 1956, as noted by the referring physician, were 5 ft. 0 in. and 79 lb. The patient had never had an interest in girls and could not recall ever having an erection. He quit school after completing the ninth grade and had done unskilled work in a factory until three years before admission. The patient's father and mother and 10 siblings attained average height. On physical examination height was 61 in.; there were partial

Fig. 5*B* (Patient 4).—All epiphyses closed. Bone, age, adult. April, 1959.

balding and evidence of muscle wasting, especially of the lower legs. Muscle biopsy and electromyelograms were characteristic of myotonia dystrophica. Buccal smear examination indicated a male chromatin pattern. Testicular biopsy revealed vacuolated Sertoli cells, hyalinization of many of the seminiferous tubules, greatly reduced spermatogenesis, and relatively abundant Leydig cells.

Comment.—This patient presented the characteristic picture of myotonia dystrophica. A brother, age 60, who was admitted at the same time also had myotonia dystrophica and similar testicular histology but was of average height (5 ft. 7 in.). The relationship of dwarfism to myotonia dystrophica and to the abnormal histology of the testes in this case is not clear.

PATIENT 5 (Figs. 6*A* and 6*B*).—A 21 9/12-year-old white single female clerical worker was referred with tentative diagnoses of endocrine deficiency and grand mal epilepsy. During the six months before admission, she had had two seizures. Birth history was negative; patient's rate of growth was slow and stopped completely at age 12 years; she had never menstruated. The patient was of good intelligence, had graduated from high school, and was employed doing office work at the time of admission. She had occasional headaches in the left temporal area. On physical examination the patient was 4 ft. 6½ in., weighed 85½ lb., and had little breast development, with sparse to absent axillary and pubic hair. A complete left hemianopsia was found on examination of the visual fields. Suprasellar calcification with destruction of the clinoids was found on x-ray examination.

Comment.—This patient presented the typical features of the pituitary (Lorain-Levi) dwarf and is the only dwarfed patient of the group presented in which a lesion of the pituitary could be demonstrated.

PATIENT 6 (Figs. 7*A* and 7*B*).—A 22 8/12-year-old white man was referred for treatment of a fractured clavicle. Birth history was normal, but development in infancy and thereafter was markedly retarded. He was given thyroid medication from the 4th to 10th year. His family noted no gain in height after age 6. He had been chronically and severely constipated since age 2 and had had recurrent prolapse of the rectum since age 7. Surprisingly, the patient managed to complete two years of high school. Family history was negative. On physical examination, height was 4 ft. 1 in.; the patient presented the classic picture of cretinism, with a dull but cheerful expression, large tongue, dry skin, protuberant abdomen, and a ventral hernia. The genitalia were infantile. Mental age was estimated at 10.8 years; I.Q., 71.

PATIENT 7 (Figs. 8*A* and 8*B*).—An 18 11/12-year-old white single woman was referred because of recurrent abdominal pain of nine months' duration. Birth history was not obtained. Patient had been very short as long as she could recall. Menarche occurred at age 11, and a regular 28-day cycle had followed thereafter. Patient had done satisfactorily in school and she was graduated from high school. On physical examination the patient was found to be 4 ft. ½ in. tall; the long bones were shortened and somewhat thickened; pelvic examination was normal except for marked flattening of the bony pelvis.

Comment.—This patient was known to have achondroplasia; she was referred for an unrelated illness.

PATIENT 8 (Figs. 9*A* and 9*B*).—A 52-year-old white male taxicab dispatcher was referred for evaluation of polycythemia and dwarfism. For five years, the patient had had recurrent dyspnea, orthopnea, and dependent edema. He was on digitalis and had been told he had "thick blood" and high blood pressure. Past history revealed that the patient had developed normally until age

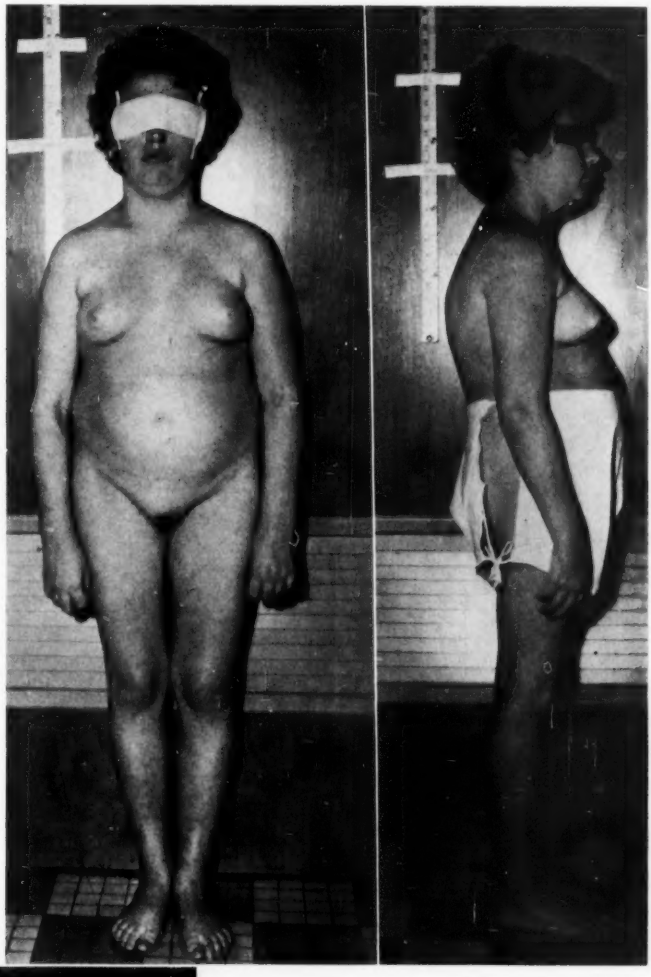

Fig. 6*A* (Patient 5).—Age 21 $^{8}/_{12}$ years. Pituitary dwarfism due to craniopharyngioma. Measured height, May, 1958, 4'6½".

Fig. 6*B* (Patient 5).—Radial and ulnar epiphyseal lines still visible. Bone age, approximately 16 years. May, 1958.

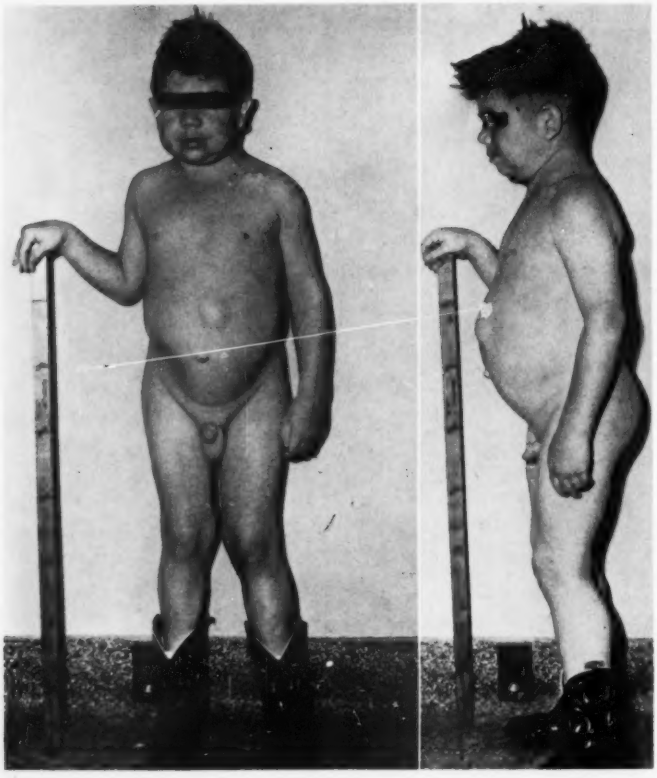

Fig. 7A (Patient 6).—Age 22 9/12 years. Cretinism. Measured height, April, 1956, 4'1".

5, when he allegedly contacted poliomyelitis. Thereafter his arms and legs failed to grow. At age 13, he weighed 39 lb. and was 3 ft. tall. Patient completed high school and business college. His libido and potentia were normal. Patient's mother and father were of normal stature, but one of seven sisters and one of four brothers have dwarfism identical to patient's. On physical examination, the patient was 4 ft. tall. The long bones were somewhat shortened, but the major reduction in stature resulted from the posterior and upward displacement of the femurs. The neck was virtually absent and there was inward displacement of the knees. In addition, the patient was hypertensive (130/100) and markedly emphysematous.

Comment.—The diagnosis in this case was made by the radiologist. Films of the two siblings were available, and the malformations of the skeleton were strikingly similar. In all three the vertebral bodies were flattened in their vertical diameter, and in each a hypoplastic vertebra was present at the dorsolumbar junction. While superficially similar to the achondroplastic dwarf, the patient with Morquio's disease presents distinct clinical and radiographic findings.

PATIENT 9 (Figs. 10*A* and 10*B*).—A 17 1/12-year-old white girl was referred because of poorly controlled diabetes. The patient had a normal birth and developed normally until age 5, when symptoms of diabetes mellitus commenced; however, almost a year elapsed before the diagnosis was

Fig. 7B (Patient 6).—Only four carpal ossification centers are present. The distal epiphysis of the ulna has appeared. Note epiphysitis. Bone age, approximately 4-5 years. May, 1956.

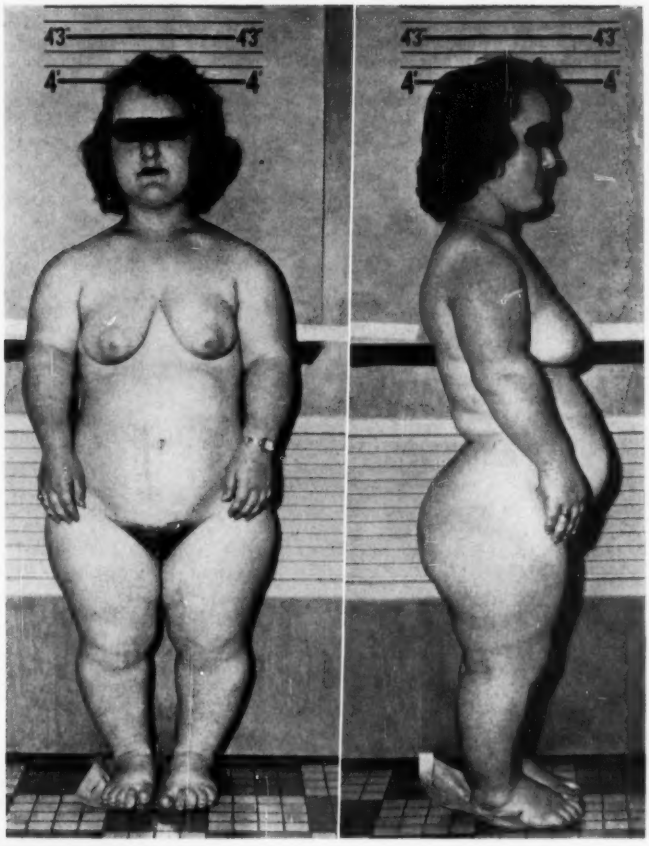

Fig. 8*A* (Patient 7).—Age 19 years. Achondroplasia. Measured height, April, 1959, 4'½".

Fig. 8*B* (Patient 7).—Note marked shortening of the phalangeal and metacarpal bones. Bone age, adult. April, 1959.

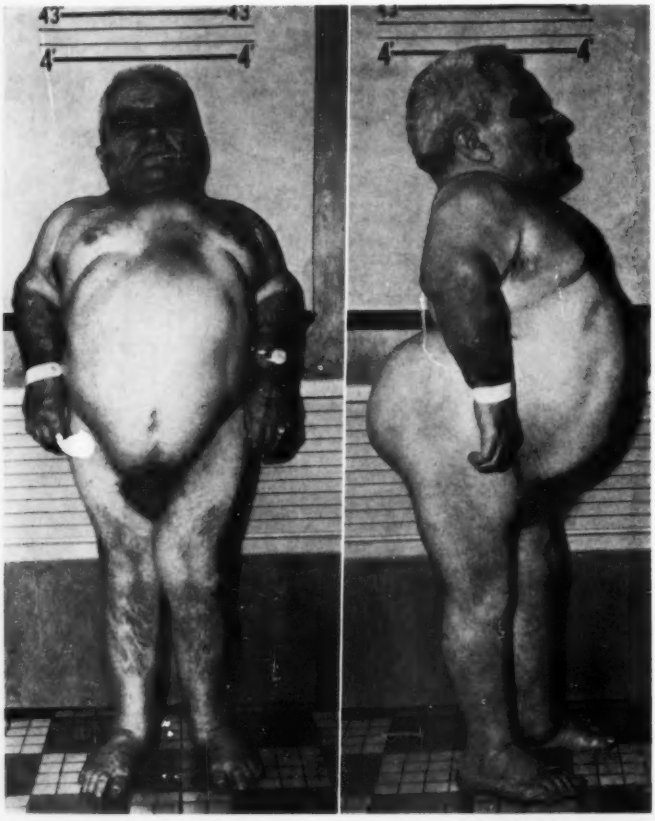

Fig. 9*A* (Patient 8).—Age 52 years. Eccentro-osteochondrodysplasia (Morquio's disease). Measured height, January, 1959, 4'0".

Fig. 9*B* (Patient 8).—Degenerative joint disease of the hands and wrist. The distal phalangeal bones are shortened. Finding consistent with diagnosis of Morquio's disease. Bone age, adult. Januuary, 1959.

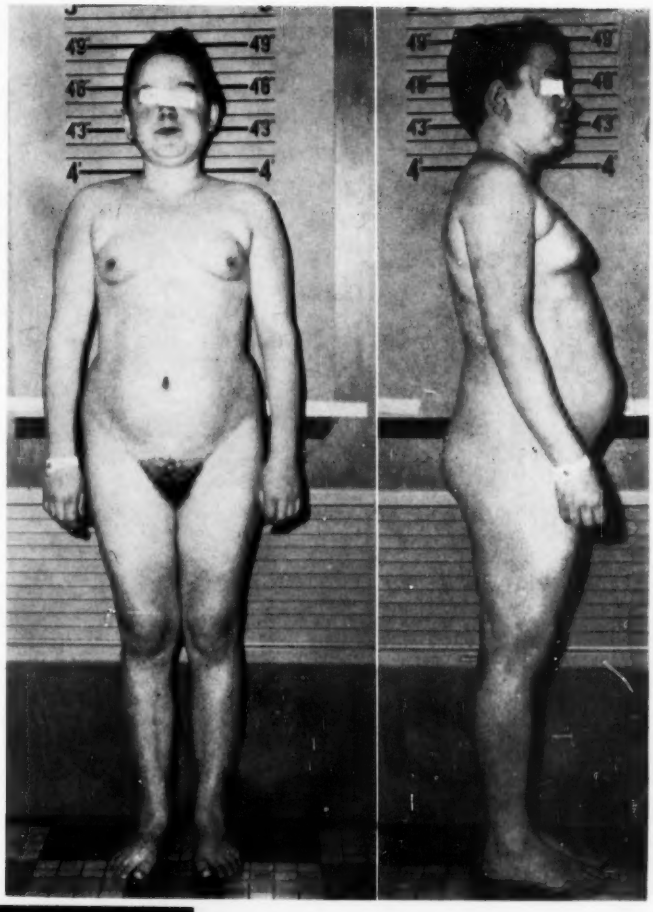

Fig. 10*A* (Patient 9).—Age 17 7/12 years. Diabetic pseudodwarfism. Photograph is a recent one. Initially, there was little or no pubic hair and the abdominal protuberance was more prominent. Measured height, April, 1957, 4'6".

Fig. 10*B* (Patient 9).—There is a rather striking degree of osteoporosis for patient's age. The epiphyses of the ulna and radia are not yet closed. Bone age, approximately 15 years. April, 1957.

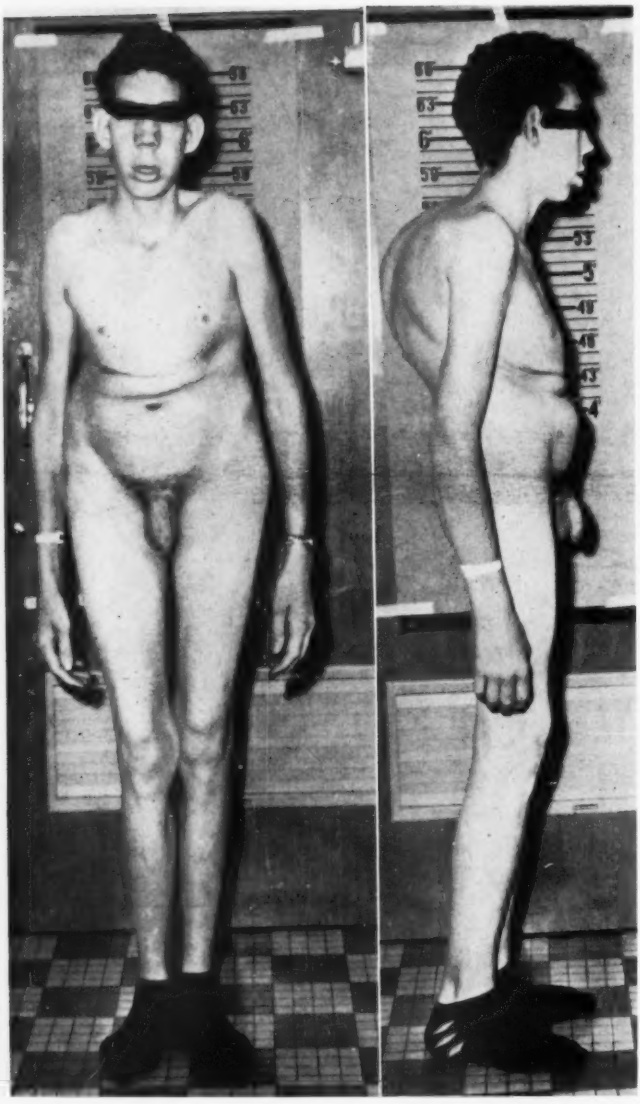

Fig. 11*A* (Patient 10).—Age 23$\frac{3}{12}$ years. Gigantism, acromegaly, and hypogonadism. Measured height, October, 1958, 6'4", span 6'9¾". Shoe size, 16EEE.

established and treatment instituted at another hospital. Shortly thereafter, the patient's family physician was killed in an auto accident, and thereafter the regulation of diet and dose of insulin were carried out by the patient's mother and later by the patient herself. She took a varying dose of regular insulin three times daily. She developed normally mentally and was doing well in school but was taken out during the third grade because her family felt school attendance was interfering with the management of her diabetes. Growth was retarded. She had not menstruated. The family history was negative for both short stature and diabetes. On physical examination the patient was 4 ft. 6 in. in height, weighed 96 lb., and appeared about age 10. There was little or no breast development, and axillary and pubic hair was sparse to absent. Additional findings included moderately severe diabetic retinopathy; sinus tachycardia, 140-160 beats per minute; protuberant abdomen, and marked hepatomegaly. Laboratory findings included a fasting blood sugar of 429 mg. %, bi-

Fig. 11*B* (Patient 10).—Excessive length and thickness of tubular bones, with tufting of the distal phalanges. The epiphyseal lines of the ulna and radia are still present. Bone age, approximately 17 years. September, 1958.

carbonate of 17 mEq. per liter, total lipids of 1,600 mg. %, and total cholesterol of 450 mg. % in the serum.

Comment.—Over the past two years the patient has been able to maintain fairly good control of her diabetes, with gratifying results in her development. She is now 4 ft. 9¾ in., and during the last four months she had had three successive episodes of vaginal bleeding at about monthly intervals. However, assays for gonadotropic activity in the urine continued to be negative. A hand-wrist film of January, 1959, disclosed that the ulnar and radial epiphyses still had not closed. This patient is an example of the stunting of growth that formerly occurred commonly among diabetic children.[9]

PATIENT 10 (Figs. 11*A* and 11*B*).—A 23 11/12-year-old white single male grocery clerk was referred with diagnoses of rheumatic fever and acromegaly. He had a normal birth, and until the age of 12 his development was not remarkable. Thereafter, his growth rate increased strikingly; he developed severe kyphoscoliosis but achieved a height of over 6 ft. by age 16. During this period of rapid growth he experienced frequent headaches and failing vision. At age 17, he was seen by a physician for an acute infection. Skull films revealed marked ballooning of the sella turcica. In 1953, he was treated with a course of x-ray therapy to the pituitary with complete alleviation of his headaches and visual symptoms. Thereafter he grew no further, and his shoe size, 16EEE, remained constant. The family history was negative. Mental development was average, although he had quit school after the seventh grade because of headaches. The patient denied

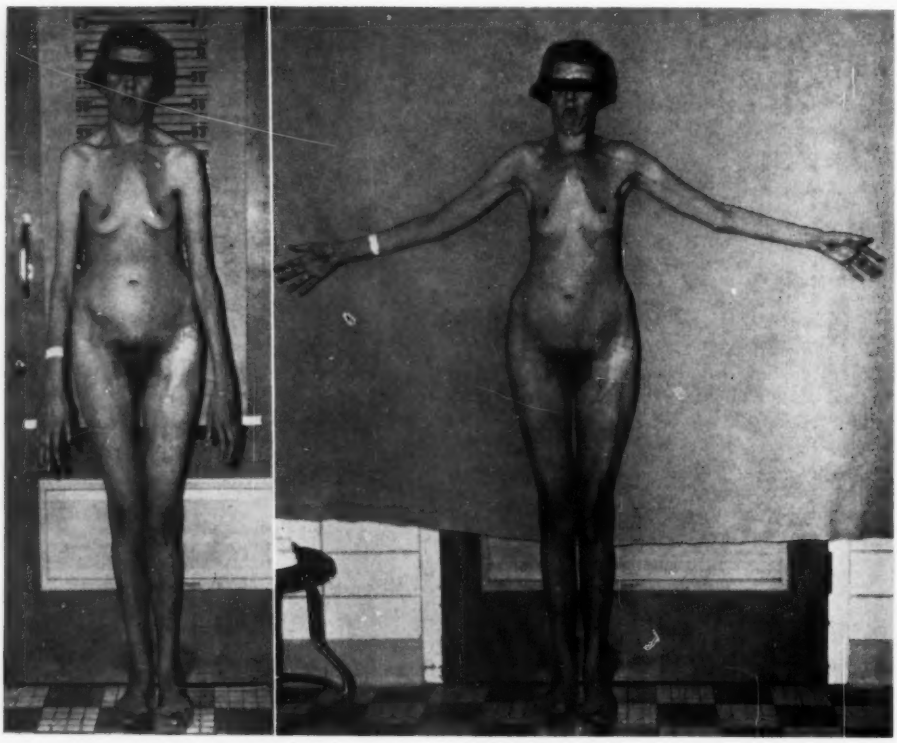

Fig. 12*A* (Patient 11).—Age 38 years. Marfan's syndrome (arachnodactyly). Measured height, December, 1958, 6'2", span 6'3½".

libido and had never had an erection or nocturnal emission. He developed some pubic hair at about the time of onset of his present illness but had not had facial hair. Physical examination disclosed a large (height 6 ft. 4 in., span 6 ft. 9¾ in., weight 205 lb.) man whose stature was deformed by severe kyphoscoliosis. The escutcheon was of the female type; axillary hair was sparse. Visual fields and acuity were normal. Testicular biopsy revealed absent spermatogenesis, vacuolation of the Sertoli cells, greatly reduced number of Leydig cells, and minimal hyalinization of the seminiferous tubules. Buccal mucosa smear showed a male chromatin pattern.

Comment.—Interpolating from the patient's span, his stature would have probably been nearly 7 ft. at the time of pituitary irradiation if the deformity of the spine had not occurred. Glove and shoe size indicated markedly excessive growth of the long bones.

PATIENT 11 (Figs. 12*A* and 12*B*).—A 38-year-old white single woman was referred because of manifestations of heart disease. Since the age of 25, she had been in a state mental institution with a diagnosis of chronic undifferentiated schizophrenia. Her birth history is unknown. Allegedly she had done well in school and at age 13 was in the eighth grade. At that time mental deterioration and emotional lability commenced and progressed steadily. She was unusually tall at age 16, but further information regarding physical development is lacking. On physical examination, the patient's height was 6 ft. 2 in., span 6 ft. 3½ in. There were prominent arachnodactyly, severe aortic regurgitation, hyperextensibility of the joints, and a pectus carinatum deformity. Subluxation of the lenses was not grossly apparent; slit-lamp examination was not done.

Comment

In Table 3 a classification of types of dwarfism recurring in the late adolescent and adult is presented. Dr. Lawson Wilkins has done a great deal to provide a rational approach to the evaluation of the dwarfed

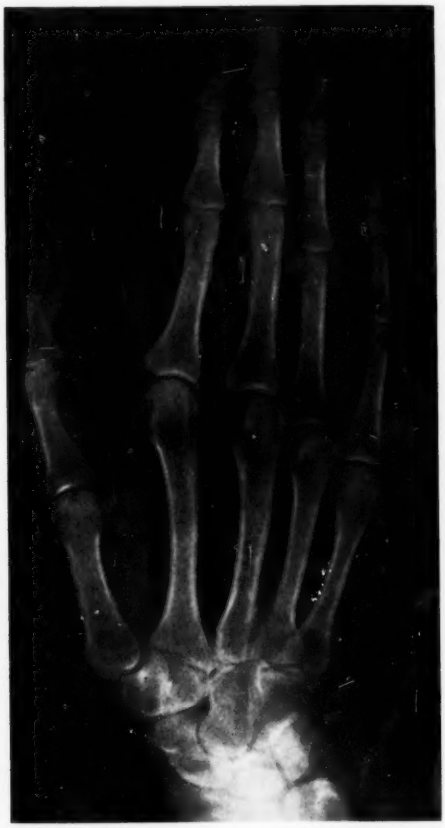

Fig. 12*B* (Patient 11).—The tubular bones are excessively elongated, producing arachnodactyly. Bone age, adult. December, 1958.

person, and the classification presented here is taken, with some modification, from his writings.[6,10] For purposes of this discussion, a dwarf is a conspicuously undersized person. No absolute figure of height can be used to define the dwarf. The subject must be considered in relation to members of his family and race of the same sex and age. The same dictum is true when considering excessive stature. The first category, heredofamilial short stature, implies no abnormality. Persons in this category achieve heights within normal limits for their family, although outside normal limits for the population as a whole. Recognition of delayed adolescence in retrospect, as in Patient 1, is not difficult. However, the diagnosis of this type of dwarfism at a younger age can be very difficult. Martin and Wilkins have recently discussed in detail the differential diagnosis of delayed adolescence, primordial dwarfism, and pituitary dwarfism.[10] The term "primordial dwarfism" is unsatisfactory in many ways, yet one would hesitate to abandon it at the present level of knowledge. Its very vagueness is a virtue. The term has been used to denote dwarfism not due to a disorder of the endocrine system. It is now recognized that endocrine disorders may coexist with dwarfism without causing it. It would seem rational to categorize cases of this type as "primordial" rather than including them under endocrine dwarfism or creating a separate category for each type.

TABLE 3.—*Dwarfism*

I.	Heredofamilial short stature
II.	Delayed adolescence
III.	Primordial dwarfism
	A. Miniature adult ("Tom Thumb" dwarf) with or without craniofacial malformations
	B. Progeria
	C. Associated with gonadal aplasia (Turner's syndrome)
	D. Associated with other major disorders
IV.	Endocrine dwarfism
	A. Pituitary infantilism (Lorain-Levi dwarf)
	B. Cretinism
	C. Precocious sexual development
V.	Dwarfism due to the chondrodystrophies
	A. Achondroplasia
	B. Eccentro-osteochondrodystrophy (Morquio's disease)
VI.	Miscellaneous causes of dwarfism
	A. Undernutrition, primary or associated with metabolic disease
	B. Tuberculosis of spine

The value of the hand-wrist film in assessing problems of stature deserves emphasis. One gains a good indication of bone age from the appearances of the secondary centers of ossification and time of closure of the several epiphyseal junctions. Further, it provides information regarding the length and thickness of the tubular bones. Recently, shortening of the fourth metacarpal (the "metacarpal sign") has been described in association with gonadal dysgenesis and short stature.[14] The precise estimation of bone age is a complex problem,[11] but for the purposes of clinical evaluation the hand-wrist film affords adequate information and seems preferable to the more elaborate

radiographic surveys which are costly and time-consuming and expose the patient to considerable radiation.

A second roentgen study that should be included in the evaluation of any problem of growth is the lateral view of the skull. This view provides information relative to the thickness of the calvarium and malformations of cranial and facial bones, as well as visualizing the sella turcica. While more elaborate techniques may be required to completely define abnormalities of the skull, the single lateral view provides an adequate screening service.

One cannot usually escape the use of the laboratory in assessing problems of stature. Tests once considered specialized are becoming widely available The functional status of the target glands, the thyroid, the adrenal cortex, and the gonads, should be assessed. Testicular biopsy, buccal smear for sex chromatin determination, and gonadotropin assay of the urine frequently provide valuable information. Unfortunately, there is no method for the direct estimation of circulating growth hormone. The serum "sulfation factor" seems to reflect growth hormone activity,[3] but the method is not generally available.

The treatment of dwarfism is generally unsatisfactory. No specific treatment is indicated in heredofamilial shortness or in delayed adolescence. Replacement therapy with those target-gland hormones that are deficient in pituitary dwarfism is indicated. Martin and Wilkins [10] have emphasized the value of early use of the sex steroids in cases of clear-cut pituitary infantilism. In the few instances in which it has been tried, human growth hormone has been effective in promoting growth in pituitary dwarfs.[12] The supply of this material is very limited. Altered bovine growth hormone has been reported effective in man in inducing positive nitrogen balance.[13] Whether this preparation will have value as a growth-promoting agent in pituitary dwarfism remains to be seen.

Dr. Theodore Keats, Professor of Radiology; Dr. Joseph Flynn, Professor and Chairman of the Department of Pathology, and the personnel of the Photoservice Department, the University of Missouri, gave assistance.

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Steroids in Rheumatoid Arthritis

A Challenge to the Internist

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The remarkable suppressive effect of adrenocortical steroids on symptoms of rheumatoid arthritis has led many patients and physicians to rely solely on these preparations. This course, fraught with dangers, is in many instances more threatening than the disease itself. Some of these hazards were recognized in the preliminary report of Hench and associates.[1] Two brief quotations from their original contribution seem especially pertinent after the interval of 10 years. "The rarity of these compounds presently and in the immediate future, and the limited scope of our preliminary data (especially regarding prolonged administration) make inappropriate now the use of the term 'treatment' except in an investigative sense. This paper is presented, not as a clinicotherapeutic report, but as a study of certain physiologic effects which these new hormones exert on rheumatoid arthritis. . . . Much more experience is needed before we shall know how effective or safe the prolonged administration of Compound E will be."

The transition from research tool to therapeutic agent occurred as rapidly as supplies of cortisone could be procured. Enthusiasm of patients and physicians over the dramatic effects of large suppressive doses led, in many quarters, to the neglect of older measures of therapy which had been useful though not spectacular. While corticosteroids now occupy a definite place in the therapeutic scheme, they do not of themselves constitute adequate treatment for this disease. More may be achieved for most rheumatoid patients if a comprehensive and individualized treatment program is initiated and maintained. The challenge to the internist in this connection is fourfold: how to insure a good basic program in rheumatoid arthritis; when to use steroids; how to control the dosage to minimize hazards, and how to manage those patients whose previous steroid dosage has been excessive.

The suggestions which follow are based on clinical experience in the Division of Arthritis of Henry Ford Hospital for the 20 years prior to cortisone and the 10 subsequent years. They are offered as a practical approach to the management of a baffling disease. No claims are made for originality, since this total program has evolved from the observations and cooperative efforts of many rheumatologists.

Basic Program

The outline of an individualized basic program presupposes a thorough diagnostic appraisal which includes not only an accurate diagnosis of rheumatoid arthritis[2] and its classification as to stage and class[3] but also a complete health inventory of the patient. The fundamentals of the basic or comprehensive program are well presented in the "Primer on the Rheumatic Diseases,"[4] under the heading Measures of Proved Value. They are also included in varying form in standard texts. Our application of these principles has been presented elsewhere in greater detail than is practical in this paper.[5]

The proper orientation of the patient and his family is the cornerstone of success in the basic program. The nature of the disease and contemplated therapy should be explained in simple but definite terms and the

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need for prolonged follow-up observation stressed. Natural remissions and exacerbations of the disease should be interpreted and mention made of sudden changes in symptoms which may follow stressful situations, emotional upsets, and undue exertion. Optimum cooperation is obtained if the goals of the treatment program are understood by all concerned. In the patient with rheumatoid arthritis these objectives are (1) relief of symptoms; (2) improvement of general health; (3) prevention of crippling, so far as possible; (4) arrest of the activity of the disease; (5) improved function of damaged joints, and (6) education in adjustment to irremediable residuals.

An initial period of hospitalization will provide symptomatic improvement and facilitate the institution of a basic program. The patient gains both physical and mental rest with release from environmental demands and an education in a program of home physical therapy. Proper resting positions should be specified. Acutely inflamed joints may be made more comfortable by rest splints in optimal position. Acetylsalicylic acid should be administered in full therapeutic dosage, usually beginning with 1.0 to 1.3 gm. (15 to 20 grains) four or five times daily, reducing the dose if tinnitus or nausea develop. Buffered preparations or enteric-coated tablets will minimize gastric irritation. Blood salicylate determinations are a reliable guide in estimating salicylate absorption; a therapeutic level between 18 and 24 mg. per 100 ml. is desirable. Additional symptomatic relief may be afforded by sedatives and hypnotics. Codeine, 30 mg. (½ grain), may be indicated occasionally if pain interferes with sleep and does not yield to non-narcotic analgesics. The *regular* use of codeine or other narcotics should not be permitted in this chronic disease. If pain is not controlled by the measures outlined above a condition other than rheumatoid arthritis should be suspected. As symptomatic relief is obtained, the dose of acetylsalicylic acid is gradually reduced, but in most patients a regular maintenance dose of 0.6 to 1.0 gm. (10 to 15 grains) four times a day should be continued.

It is generally recognized that rheumatoid arthritis is a constitutional disease with joint manifestations. Following the comprehensive examination, any evident departures from an ideal health pattern should receive attention. The diet should be well balanced, high in protein and in protective foodstuffs, with calories suited to the patient's needs. Vitamins and mineral supplements may be employed if indicated, but it should be made clear that there is no dietary plan or vitamin preparation which has specific value in rheumatoid arthritis. Focal infections are not thought to alter the course of the disease. However, any focus of acute or chronic infection should be eradicated as a contribution to better health. Rest is the most important general measure, even after the subsidence of acute symptoms, and the number of hours should be specified for each patient.

Local measures of treatment encompass simple physical therapy, daily therapeutic exercises, and the use of intra-articular steroids for refractory joints. A critical factor in minimizing joint deformity is the patient's willingness to adhere to a daily routine of carefully planned physical therapy. Daily housework is not a substitute for a specific therapeutic exercise program. Best results are obtained if heat is applied prior to exercising the joints. This may be accomplished by use of dry heat (infrared lamp, heating pad) or moist heat (compresses, hydrocollator packs, or water baths). Paraffin dips for hands and wrists are an excellent means of applying moist heat. Simple printed instructions, such as the booklet Home Care in Arthritis,[6] will insure proper application of these principles of physical therapy. At times, in spite of a diligent daily exercise program, contractures and later subluxations may develop. Splints and rest casts offer great assistance in preventing these complications. Intra-articular injection with hydrocortisone tertiary-butylacetate or one of the newer analogs may add greatly to the patient's comfort. Absolute aseptic technique in such procedures is mandatory, and injec-

tion therapy is contraindicated in a joint in which there is any suspicion of infection.

The foregoing measures, which constitute the basic or conservative program of therapy, have stood the test of time, and are easily omitted because they seem old-fashioned. However, many patients have achieved a satisfactory remission or control of rheumatoid arthritis solely by this basic program. It is the general plan of living to which the rheumatoid patient must adhere for an indefinite period, often for life, with modifications in details from time to time.

Supplemental Program

If, however, objective as well as subjective improvement is not evident in 6 to 12 weeks, the physician should ask himself three major questions. First, has the patient actually been following all details of the treatment conscientiously? Second, is the diagnosis accurately established?[2] (Other rheumatic diseases, as well as disorders in which joint manifestations are secondary, may present with a clinical picture suggestive of rheumatoid arthritis.) If these questions can be answered affirmatively, the third query, then, is, what supplemental measures should be considered?

The most commonly used supplemental medications are organic gold salts, adrenocortical steroids, phenylbutazone, and antimalarial drugs. None of these drugs replaces the basic program, which must be continued in any event. Each of them entails not only additional expense but, more important, added hazards to the patient. These hazards must be weighed against the risks of allowing a potentially crippling disease to proceed unabated. Since this paper deals primarily with the use of steroids in rheumatoid arthritis, discussion of the other drugs is omitted. However, we are of the opinion that all patients with *active* rheumatoid arthritis deserve an early trial of gold therapy when supplemental medication is indicated.

Corticosteroids as Supplemental Therapy

Numerous factors are to be considered in determining whether or not to use corticosteroids in a particular rheumatoid arthritis patient. Some situations which lead us to institute this supplemental measure are as follows:

1. The patient who has rapidly progressive disease which has shown an inadequate response to a conscientiously followed basic program.

2. The patient with active disease for whom it is not economically feasible to adhere to a prolonged period of inactivity and absence from his customary vocation. In considering this factor, one must be mindful of the calculated risk of suppressing symptoms of rheumatoid arthritis to permit overuse of diseased and damaged joints.

3. The patient who needs additional improvement in functional capacity in order that he may more adequately participate in the daily program of therapeutic exercises and other physical therapy. The need for steroids should not be governed by unrealistic demands of the patient but based on sound objective as well as subjective evaluation.

Even the rheumatoid patient of the above three groups is not committed to corticosteroid therapy before the relative contraindications are reviewed in connection with the specific case. Certain coexisting diseases, known to be aggravated by steroids, will require close medical control. Such conditions include diabetes mellitus, peptic ulcer, and edema from whatever cause. Other conditions which may be partially or wholly uncontrollable are represented by patients with a history of previous untoward effects from steroids (provided a realistic dosage schedule had been followed), those with a history of psychiatric disorder, those with severe grades of osteoporosis, and those with infections not amenable to specific antibiotics. Patients with prior tuberculous infection should, as a rule, be spared steroid therapy. If it is deemed essential, adequate concomitant antituberculous treatment is mandatory. Isonicotinic acid amide, 100 mg. t.i.d., should be given throughout the period of steroid administration.

Having decided to use steroids as a supplement to the basic program, the physician must settle the question of type of drug and dosage. In spite of the great number of brand names (with as many as six copyrighted names for the same chemical compound in some instances), there are fundamentally only three groups of corticosteroids as far as antirheumatic effect per milligram is concerned, as shown in the following tabulation. Cortisone and hydrocortisone are roughly equivalent; prednisone and prednisolone are approximately four or five times as potent as hydrocortisone, with methyl prednisolone and triamcinolone a trifle more so; the newest, dexamethasone, is probably 6 to 8 times as potent as the prednisolone group or 30 to 40 times as powerful as hydrocortisone. Each of these preparations has its advantages and each its disadvantages. With some notable exceptions, each in equivalent antirheumatic dose will have equal proclivity to produce undesired effects, although there is variability in the type of such effects. For each it is axiomatic that as the dose increases, so do the hazards. The clinician will do well to become thoroughly familiar with what can be accomplished with the preparations in longest use. The current practice of skipping about to each new compound as soon as it becomes available, without awaiting the results of investigations of such drugs for at least a year in research centers, seems imprudent.

Cortisone	25 mg.
Hydrocortisone	20 mg.
Prednisone	5 mg.
Prednisolone	5 mg.
Methyl Prednisolone	4 mg.
Triamcinolone	4 mg.
Dexamethasone	0.75 mg. (?)

The situation is further complicated by the multitude of combinations in which the steroids are now appearing—combinations with salicylates, with phenylbutazone, with antacids, with tranquilizers, with vitamins—each labeled with its own trade name which too often masks the fact of steroid content. The use of one or another of these "shotgun" preparations is governed by a thorough realization of the type and amount of steroid in each tablet. The fixed ratio of the various ingredients in such combinations is fallacious and should not otherwise limit therapy. Additional salicylate will usually be needed to obtain therapeutic levels.

There is still a considerable divergence of opinion as to the manner in which steroids should be used in rheumatoid arthritis. Granted they are life-saving in many acute conditions, have remarkable suppressive and analgesic properties when used in relatively large doses, and are excellent aids in meeting crises, there is not one which when used over a long period in patients with rheumatoid arthritis does not produce adverse or unwanted effects. Some rheumatologists believe in the initial use of large suppressive doses, with subsequent reduction as possible. Others advise against using these agents in a chronic disease such as rheumatoid arthritis, since, so far as is now apparent, they do not fundamentally alter the progress of the disease and may actually contribute to more rapid joint deterioration by suppressing discomfort and allowing overuse of diseased joints. We agree with those who advocate commencing therapy with low doses. Too often the patient who has once experienced the miraculous relief afforded by large initial steroid doses is most unhappy when this dose must be reduced.

Control of Dosage to Minimize Hazards

The only way to minimize unavoidable hazards is by careful regulation of dosage. Amounts which in the beginning may be ineffective can be gradually increased to arrive at the smallest dose which gives a reasonable degree of relief in addition to that provided by the continuing basic program. Hazards of full suppressive doses are explained to the patient, and he is encouraged to be grateful for partial amelioration of symptoms. The total daily dose should be given in fractions either three or four times a day, tailored to the patient's symptom pattern. As an example, if it is decided to start steroid supplements with a dose of 4 mg. of prednisolone daily and the patient has great-

est discomfort in the morning, the first dose of the day might be 1.5 mg., the second 1 mg., then 0.5 mg. and 1.0 mg. as subsequent fractions. If a few days' trial of this schedule proves it to be inadequate, slight increases may be made as indicated. Often an early morning dose given one-half to one hour before arising is effective. As a precaution against gastrointestinal complications, it is wise to give each dose of steroid with antacid or milk or with a meal.

If chronic hypercortisonism or other unwanted effects are to be minimized, most workers believe that there are total daily doses of corticosteroids which should not be exceeded in rheumatoid arthritics who may be taking these drugs for indefinitely long periods. Opinions vary somewhat as to the maximum doses tolerated in the three steroid categories, and it must be realized that there are individual variations in patients as to their tolerance. Men seem to handle larger doses than women, and premenopausal women slightly larger doses than postmenopausal. A useful guide in estimating the maximum desirable daily dose for sustained administration to patients with rheumatoid arthritis is illustrated in the tabulation given at the bottom of this page.

Suppression of normal adrenal responsiveness is an attendant hazard of corticosteroid therapy which must not be overlooked. A patient who is receiving steroids or has had them within six months needs the support of increased steroid dosage during such periods of added stress as operation, accident, or acute illness. Such support may be afforded by increased oral dosage or, at times, by intramuscular or intravenous administration as indicated. Ideally, each patient taking steroids should carry on his person a card stating the type and dosage of steroid he is using. Such a precaution may be lifesaving in case of emergency.

Undesired Effects of Corticosteroids

A brief review of some of the undesired effects of use of steroids is illustrated by patients seen recently in whom overreliance had been placed on these drugs. Among the obvious adverse effects is the development of a Cushingoid state—the so-called "Iatrogenic Cushing's syndrome." This is well represented by a 14-year-old juvenile rheumatoid patient (Fig. 1) who had been receiving 200 mg. of hydrocortisone daily. Evident is the moon facies; the truncal obesity, the supraclavicular pads and the wasting of the extremities are also characteristic. The back brace was necessitated by collapse of four thoracic vertebrae because of osteoporosis. Facial rounding is evident in a woman of 29 (Fig. 2) who had received cortisone for one year and prednisone, 15 mg. daily, for one year; the improvement resulting from gradual withdrawal of steroids while instituting the basic program supplemented by chrysotherapy is evident in Figure 3, approximately 10 months later. Hirsutism and acne (Fig. 4) are well demonstrated in a girl of 17 who had received cortisone for one year and 20 mg. of prednisone daily for eight months. Her appearance two years later on the basic program supplemented by 30 mg. of hydrocortisone daily is shown in Figure 5. Striae (Fig. 6) may be marked at times in steroid-induced Cushing's syndrome.

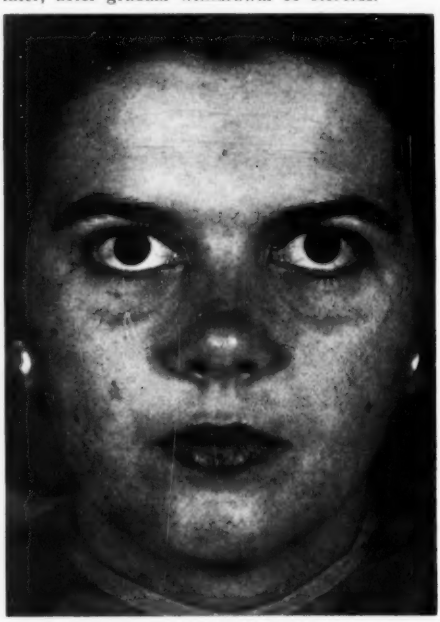
The most insidious adverse effect is the development of the clinical picture of hypercortisonism (Fig. 7) described by Slocumb [7] and associates, characterized by profound cyclic fatigue, psychic mood swings, and myalgia and arthralgia without objective changes. Osteoporosis may lead to vertebral compression (Fig. 8) with or without significant preceding trauma, as in this 29-year-old woman. A large gastric ulcer (Fig. 9) may develop asymptomatically and go un-

	Hydrocortisone, Mg.	Prednisone, Mg.	Dexamethasone, Mg.
Adult male	40	7.5	1.0 (?)
Adult female	30	5.0	0.75 (?)
Postmenopausal female	25	4.0	<0.75 (?)

Fig. 1.—Cushingoid state in 14-year-old girl receiving 200 mg. hydrocortisone daily.

Fig. 2.—Facial rounding; age 29; cortisone for one year followed by prednisone, 15 mg. daily, for one year.

Fig. 3.—Same patient as Figure 2, 10 months later, after gradual withdrawal of steroids.



recognized until severe hemorrhage occurs, as happened in a woman of 27 who had been taking 10 mg. of prednisolone daily for three years, with previous use of other corticosteroids for four years. Occult sepsis (Fig. 10) is represented by this staphylococcal arthritis of the hip in a woman of 64 who had been treated with 20 mg. of prednisone daily for 10 months. Purpura and ecchymoses (Fig. 11) may become more marked than in this illustration and are prone to occur in anyone

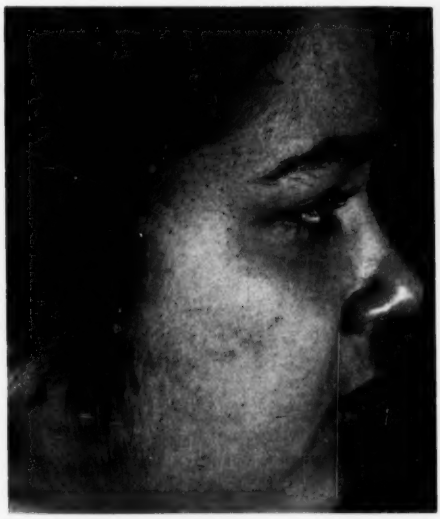


Fig. 4.—Hirsutism and acne; age 17; cortisone for one year and prednisolone, 20 mg. daily, for eight months.

Fig. 5.—Same patient as Figure 4, two years later, on 30 mg. hydrocortisone daily.

on long-term steroid therapy, especially postmenopausal women. Other adverse effects, more difficult to picture, include development of diabetes mellitus, psychiatric disturbances, reactivation of infections, hypertension, and edema.

These are not pretty pictures. They are presented as graphic illustrations of the un-

Fig. 6.—Striae; same patient as Figure 4.

Fig. 7.—Hypercortisonism; sketch suggesting cyclic fatigue and mood swings.

toward effects of a group of potent drugs, adrenocortical steroids. Overdosage with these drugs, while not as acute or dramatic as that seen with, say, morphine or digitalis, may prove equally disastrous. Like most therapeutically useful agents, steroids possess inherent features which limit their application.

Treatment of Hypercortisonism

Perhaps the most difficult challenge to the internist is presented by the patient who, when first seen by him, is in a state of hypercortisonism induced by previous therapy. Such a patient must be told tactfully but firmly that a change in program is now indicated which will require the utmost in cooperation on his part. Again a period of hospitalization proves helpful, with full-scale basic or conservative program including salicylates to tolerance. Extra rest, often 12 to 14 hours a day, with enough therapeutic exercise to preserve joint mobility is necessary. The patient must understand the importance of tolerating withdrawal symptoms, such as increased fatigue and mental depression. Anxiety is treated with tranquilizers or sedatives.

Fig. 8.—Osteoporosis with partial collapse of 12th thoracic vertebra; same patient as in Figure 2.

Fig. 9.—Gastric ulcer, antral; woman of 27; prednisolone, 10 mg. daily, for three years; other corticosteroids for four years previous.

The decrease in total daily steroid intake must be gradually accomplished. If the dose which induced hypercortisonism was relatively large, (60 to 80 mg. of hydrocortisone or 15 to 20 mg. of prednisone), the daily ration may be cut at first by 10 mg. of hydrocortisone or 2.5 mg. of prednisone and the balance given in divided doses at six- or eight-hour intervals. After adjustment to the lower steroid dosage, usually in four to seven days, a further similar decrement is made. When the total daily dose is at the level of

Fig. 10.—Occult sepsis, staphylococcal arthritis of hip; woman of 64; 20 mg. prednisone daily for 10 months.

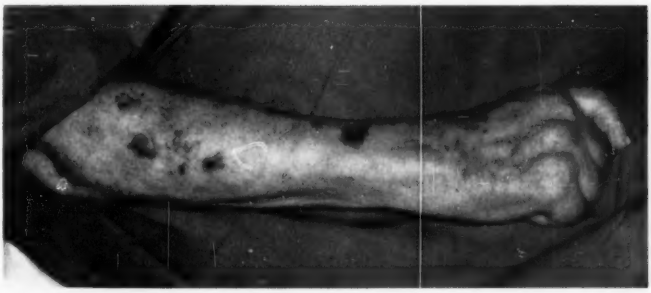


Fig. 11.—Purpura and ecchymoses; woman of 72, on steroid therapy for six years.

40 to 50 mg. of hydrocortisone or 10 to 12 mg. of prednisone, the decrement should be smaller, (5 mg. of hydrocortisone or 1 mg. of prednisone) and the interval between decreases 7 to 14 days. Dosage of less than 30 mg. of hydrocortisone or 7.5 mg. of prednisone may necessitate decrements approximating 2.5 mg. of hydrocortisone or 0.5 mg. of prednisone and intervals for adjustment prolonged to 10 to 20 days or longer. Patience and perseverance are the watchwords.

At any time in this withdrawal period, constitutional symptoms, such as febrility, increased stiffness and muscle pains, or abrupt increase in lassitude and weakness may dictate a return to the prior level until adjustment has occurred. After such an episode, more gradual withdrawal will probably be successful. Adequate treatment of hypercortisonism may require six months to two years and cannot be hurried without undue risk of provoking a severe exacerbation of the underlying rheumatoid process. As Slocumb [8] says, the "treatment of hypercortisonism is more difficult than its prevention."

Comment

The challenge intrinsic in steroid administration, the potential benefit versus possible adverse effect, is acceptable. It should not deter the proper usage of these drugs in a crippling disease. Despite the foregoing drawbacks, steroids, used with due caution and watchful attention, have a definite place as a drug supplement in rheumatoid arthritis. Their beneficial effects may greatly facilitate patient care when additional therapeutic efforts are concretely indicated. Until more effective and safer agents are discovered, their use in selected cases seems warranted.

The clinician, however, should not be lulled into a false sense of security. It is important for him to remember that whenever corticosteroids are employed in rheumatoid arthritis, whatever product or dose is selected, he is doing little more than suppressing some manifestations of a disease which may be progressing in spite of symptomatic improvement. Steroids can not prevent all joint damage, nor can they be expected to return a damaged joint to normal. They are a part, not the whole, of comprehensive management in rheumatoid arthritis.

Summary

The importance of the basic or conservative program of treatment for rheumatoid arthritis is stressed. A workable plan for the application of such a program is offered.

Adrenocorticals, as a supplemental part of this program, have a place in the treatment of rheumatoid arthritis.

Detailed consideration is given to the indications and contraindications to their use as supplements.

Hazards associated with prolonged steroid administration to patients with rheumatoid arthritis are illustrated, and measures to minimize such adverse effects are discussed.

The management of the patient whose rheumatoid arthritis has been complicated by induced hypercortisonism is outlined.

Division of Arthritis, Henry Ford Hospital (2).

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Thyrotoxicosis Treated with Small Repeated Doses of Radioiodine

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With the Assistance of Other Members of the Thyroid Clinic *

An ultimate objective in the treatment of hyperthyroidism with radioactive I^{131} has been to develop a method of selecting for each patient a dose of the isotope which will destroy precisely enough thyroid tissue to produce the euthyroid state. The application of such a method would eradicate the therapeutic sequelae of radiation thyroiditis, thyroid storm, and myxedema. Protraction of the hyperthyroid state would not occur in patients who now require supplementary doses to correct for the inadequacy of the initial attempt.

Although a search for a satisfactory method of dose prediction has been in progress since radioiodine was first used, in 1941, in the Massachusetts General Hospital,[5] no ideal solution has yet been found. The thyroidal uptake of I^{131} can be measured by tracer doses of the isotope, but the mass of the thyroid gland can only be estimated with great error, either by palpation or by the use of the scintogram. Furthermore, it seems likely that variable reactions of the acinar cells of the gland are not adequately reflected by the scintogram. As a result, each group of workers has evolved a different system of treatment based upon its clinical experience. The selection of patients for treatment with I^{131} is not uniform. Criteria for evaluation of thyroid function vary both for clinical signs and laboratory tests. The time intervals between supplementary treatments are considerably different from clinic to clinic. The follow-up period of treated patients depends upon local convenience. Disagreement concerning the desirable ratio between the number of patients overtreated and undertreated has led to a variety of dosages of I^{131}.

The multiplicity of dosage systems, together with the current concern for excessive radiation of all kinds, encourages us to record our experiences in giving somewhat smaller doses of I^{131} than have been reported in most series of patients.

Care of the Patients

The Thyroid Clinic of the University Hospitals was organized in 1949, and has been functioning since at an accelerating rate. The annual numbers of patient-visits for all types of thyroid disease were 280 (1950), 370 (1951), 523 (1952), 550 (1953), 597 (1954), 731 (1955), 773 (1956), and 900 (1957). Most of the patients were born in Iowa, although a minority are natives of Western Illinois. Caucasian stocks predominate; less than 1% are Negroes. The great majority are ambulatory and are treated as outpatients, either indigent or private.

Each patient is first examined in the clinical service to which he or she is admitted. A physician takes the history, makes the physical examination, and secures

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* Edward E. Mason, M.D., and Joseph A. Buckwalter, M.D. (Department of Surgery), and Higdon B. Elkins, M.D. (deceased), formerly of the Department of Radiology.

appropriate laboratory tests which include the basal metabolic rate (BMR), the protein-bound iodine of the blood serum (PBI), and the thyroidal uptake of I^{131} at 4 hours and 24 hours (I^{131} uptake). He then presents the patient at the weekly session of the members of the Thyroid Clinic. There the findings are reviewed; the patient is examined for pertinent physical signs. External examination of the eyes and measurements with the exophthalmometer are made uniformly by the same person. The diagnosis and treatment are discussed. Finally recommendations for treatment are made and usually accepted by the patient's physician. Suitable records for each patient are kept for the Clinic.

The members of the Thyroid Clinic represent the departments of Internal Medicine, Surgery, Radiology, and the Radiation Research Laboratory. Some have served in this clinic for 10 years, and all have accumulated considerable experience in thyroid disease.

Indications for I^{131} Therapy.—Patients are treated for thyrotoxicosis with I^{131} unless the goiters are estimated to weigh over 100 gm. or the glands contain nodules thought probably malignant. There is no restriction for age or sex. Pregnancy is an absolute contraindication.

Dosage of I^{131}.—The dose of radioiodine is calculated to deliver between 60μc. and 80μc. per gram of thyroid tissue in 24 hours. Two or more members of the Thyroid Clinic estimate the weight of the gland by palpation. The probable uptake of a dose of I^{131} is calculated to be equal in percentage to that of the 24-hour uptake of a 30μc. tracer dose, measured the day before treatment. The smaller doses in the range are given to younger patients with diffuse goiters and the larger doses to older patients with nodular goiters. For example, a diffuse goiter, estimated to weigh 40 gm., with a 24-hour uptake of 75% of the tracer dose, would be given the dose indicated by the following calculation:

$$60\mu c. \times \frac{100}{75} \times 40 = 3.2 \text{ mc.}$$

Besides the error of estimation of gland weight by palpation, it is also recognized that perhaps half the goiters judged to be diffuse actually contain small nodules which require more radioiodine. Large nodular glands are frequently given more than the stated range, especially when the initial therapeutic dose has been shown to have been ineffective. It is singularly difficult to determine by palpation whether masses recurring after thyroidectomy are hyperplastic or adenomatous, particularly when the pathologist's report on the extirpated gland is not available.

Routine Observation of Patients.—After administration of the initial therapeutic dose of I^{131} a 24-hour measurement of the thyroidal uptake is made. The percentage uptake usually corresponds closely with that of the tracer dose, given two days before. The patient is instructed to return in three months. Resumption of normal activity is permitted if the patient feels able. On each succeeding visit the patient is again examined by his or her physician, who secures tests of the BMR, the PBI, and the I^{131} uptake. When the results are available, he again presents the patient at a session of the Thyroid Clinic, where the case is reviewed and the patient examined. The eyes are again measured. If the group decides that physical signs or laboratory findings of hyperthyroidism still persist, another therapeutic dose of I^{131} is given. This procedure is repeated at three-month intervals until one year has elapsed after the last therapeutic dose of radioiodine or until permanent myxedema from I^{131} has been demonstrated. Patients are not routinely followed after this time, but they are instructed to return if symptoms recur. Rarely patients have developed myxedema more than one year after a therapeutic dose of I^{131}, but the incidence has not been established by systematic observation.

Demonstration of Permanent Myxedema from I^{131}.—When the patient returns three

months after a therapeutic dose of I^{131}, we have frequently observed a decline in the thyroidal uptake of I^{131} to less than 10% in 24 hours. The values for the PBI and BMR are usually not correspondingly diminished. We have termed this finding the "post-therapeutic suppression" of the thyroid gland. Usually in another three months the function studies have risen to normal values. Signs of myxedema may or may not have appeared. Whenever signs and symptoms of frank myxedema do occur, a vigorous attempt is made to persuade the patient to tolerate the condition without treatment for several months. We have seen recovery to the euthyroid state occur spontaneously six months or more after thyroid suppression has produced clinical myxedema. During recovery the thyroidal uptake of I^{131} rises before amelioration in the signs or symptoms; this laboratory finding can be the basis of a confident prediction of recovery.

If the myxedematous state has persisted for six months or the patient insists on treatment before that time, we classify the case as permanent myxedema and start the administration of desiccated thyroid or triiodothyronine in full doses. In this instance, there is rarely necessity for cautious therapy with small doses because the patient's coronary vessels and adrenal glands have been fully tested by thyroid hormones only six or eight months before.

The Series of 338 Cases

Selection.—To date (March, 1959) we have had 854 patients in whom the diagnosis of thyrotoxicosis has been made. The diagnostic criteria have been the symptoms, physical signs, and thyroid function tests. The incidence of symptoms and signs are stated in Table 1.

Of 854 cases, 165 (19.3%) have had thyroidectomy and 689 (80.6%) have been treated with I^{131}. The records of all cases in which I^{131} had been given were reviewed in March, 1958, and 338 patients were selected for this series solely because they were all who had been observed in the Thyroid Clinic to be euthyroid for more than six months or had developed permanent myxedema from therapy. The great majority of cases rejected from the series concerned patients who had not returned for adequate observation. The large number of omitted cases can be explained by the fact that they were mostly indigent patients who had to travel as far as 350 miles to reach the hospital. Their transport and care were determined by the authorities of their counties of residence. The proportion of private patients with adequate periods of observation was much higher.

Age of Patients in the Series.—The distribution of patients in the series according to their ages in decades is recorded in Table 2. The greatest number occurred in the dec-

TABLE 1.—*Incidence of Symptoms and Signs in Eight Hundred Fifty-Four Cases of Thyrotoxicosis*

Symptoms	No.	%	Signs	No.	%
Cardiac palpitation	745	87	No goiter	47	6
Tremor of the fingers	647	75	Goiter *	807	94
Nervousness	628	73	Tachycardia	745	87
Loss of 15 lb. or more	403	47	Soft skin & hair	712	83
Intolerance to heat	394	46	Tremor of fingers	647	75
Increased fatigability	316	37	Apparent proptosis	384	45
Excessive hunger	211	24	Onycholysis	178	20
Dysphagia	101	11	Cardiac arrhythmias	163	19
Diarrhea	79	9	Myopathy	78	9
Myasthenia	78	9	Pretibital myxedema	6	
Depression	51	5			
Hoarseness	37	4			

* Goiters were classified as 428 diffuse, 197 nodular, 106 post-thyroidectomy, 38 retrosternal, 23 solitary nodular, 5 thyroiditis, 3 carcinoma, 2 colloid, 4 others.

TABLE 2.—*Age of Patients in Series of Three Hundred Thirty-Eight*

Age, Yr.	No. Patients
0-9	0
10-19	10
20-29	37
30-39	81
40-49	72
50-59	69
60-69	48
70+	21
	338

ade of 30 years to 39 years, but nearly as many were in each of the two following decades and 21 patients were over the age of 70 years. The incidence of nodular goiter was much greater in the group over the age of 40 years.

Type of Goiters Irradiated.—Of the 338 patients in the series, 199 (58%) were classified as having diffuse goiters, 62 (18%) had nodular goiters, 53 (15%) had goiters recurring after thyroidectomy (in most of which it was impossible to determine whether the glands were diffuse or nodular), and in 24 (7%) examiners disagreed on the type of gland or could palpate no thyroid tissue.

Thyroid Function Tests.—At each examination of a patient, determinations were made in the hospital laboratories of the BMR, the PBI, and the thyroidal uptake of I^{131} in 4 hours and 24 hours, after a tracer dose of 30μc. of the isotope. The ranges of normal in our laboratories are BMR, +15% to −15%; PBI, 3.5μg. to 8.0μg. per 100 ml.; I^{131} uptake, 15% to 45% in 24 hours.

In making the diagnosis of thyrotoxicosis from the symptoms, signs, and function tests, it was found that the BMR was the least reliable and least diagnostic of the three tests of thyroid activity. The results of the PBI and I^{131} uptake, however, were frequently distorted by the ingestion of iodine or the many drugs and hormones described in the literature. The members of our group have been reluctant to depend on any single type of laboratory test for diagnosis after encountering many patients in whom discrepancies occur and one test proves more revealing than another. The distribution of the laboratory values in the series are seen in Table 3.

Results of Therapy with I^{131}.—The results of therapy in the series of 338 patients are summarized in Table 4. With the doses of I^{131} previously described and the periods of observation practiced in our clinic, 205 patients (60%) achieved the euthyroid state or developed permanent myxedema with a single dose of the isotope. Most of the patients requiring three or more doses had nodular goiters. They also required higher single doses than the average of the series. The over-all incidence of permanent myxedema in this series was 9.1%. According to gland type, the distribution was as follows: in 202 diffuse goiters, 19 (9.4%); in 61 cases of nodular goiter, 4 (6.5%); in 75 post-thyroidectomy patients or those without palpable goiters, 6 (8%). Two other cases of myxedema were not classified as to gland type.

Time to Attain Euthyroid State After Initial Therapy.—An important problem in the treatment of thyrotoxicosis is the length of time the disease goes uncontrolled after therapy is begun. A lag period occurs in

TABLE 3.—*Initial Values of Thyroid Function Tests*

BMR, %	Cases	PBI, μg/100 Ml.	Cases	I^{131} Uptake % in 24 Hr.	Cases
−14- −10	1	0- 2.0	0	16- 20	4
− 9- 0	3	2.1- 4.0	1	21- 25	2
+ 1- + 5	7	4.1- 6.0	5	26- 30	5
+ 6- +10	6	6.1- 8.0 •	14	31- 35	6
+11- +15•	13	8.1- 10.0	39	36- 40	10
+16- +20	32	10.1- 12.0	54	41- 45 •	10
+21- +25	17	12.1- 14.0	74	46- 50	17
+26- +30	45	14.1- 16.0	56	51- 55	23
+31- +35	37	16.1- 18.0	33	56- 60	31
+36- +40	30	18.1- 20.0	16	61- 65	28
+41- +45	30	20.1- 22.0	18	66- 70	30
+46- +50	28	22.1- 24.0	6	71- 75	41
+51- +55	15			76- 80	42
+56- +60	17			81- 85	21
+61- +65	11			86- 90	40
+66- +70	8			91- 95	13
+71- +75	6			96-100	10
+76- +80	3				
above +80	4				

• Represents high "normal values."

TABLE 4.—*Results of Therapy with I^{131}*

No. Doses of I^{131}	Patients Treated		Euthyroid State	Permanent Myxedema		Irradiation Thyroiditis	Thyroid Storm
	No.	%		No.	%		
1	205	60	178	26	12	0	1
2	89	26	84	5	5	0	0
3	26	7	26	0		0	0
4	11	3	11	0		0	0
5	4		4	0		0	0
6	2		2	0		0	0
10	1		1	0		0	0
—	—	—	—	—	—	—	—
	338		307	31	9.1	0	1

treatment either by thyroidectomy or with the use of I^{131}. Preparation for surgery sometimes occupies many months in bringing the patient to the euthyroid state with antithyroid drugs. When the patient requires multiple doses of radioiodine at intervals of three months, it is probable that the total elapsed time before permanent euthyroidism is achieved is longer than when thyroidectomy is performed. However, in most patients receiving I^{131} the protracted period of hyperthyroidism is characterized by some or much amelioration of symptoms and a decline in the metabolic rate. The time relations for the series are summarized in Table 5. It should be noted that in 34% of the series the euthyroid state was attained in three months after initial therapy. Sixty-three per cent of the patients were controlled in six months. This time compares favorably with the experience in thyroidectomy.

TABLE 5.—*Time in Attaining Euthyroid State After Initial Dose of I^{131}*

Mo.	Patients	
	No.	%*
1- 3	114	34.6
4- 6	94	28.5
7- 9	42	12.7
10-12	21	6.3
13-15	28	8.5
16-18	8	2.4
19-21	11	
22-24	2	
25-27	3	
28-30	3	
31-33	2	
24-36	1	

* Percentages based on 329 patients.

Magnitude of Single Doses of I^{131}.—In the series of 338 patients the arithmetic mean of the single administered doses of I^{131} was 4.6 mc.; the mode was 4.0 mc. The range of 3.0 mc. to 6.0 mc. included 67% of all doses given; 90% of the doses were included in the range from 1.0 mc. to 8.0 mc.; all doses were within the limits of 1.0 mc. to 15.2 mc.

Total Dosage of I^{131} per Patient.—The total amount of I^{131} administered to each patient to achieve the euthyroid state or permanent myxedema can be readily computed and compared with the reports of other workers. At least, these data show the maximal radiation to which patients are exposed at any time. (Table 6).

TABLE 6.—*Total Dosage of I^{131} Given per Patient* *

I^{131}, Mc.	Diffuse Goiters		Nodular Goiters	
	No.	%	No.	%
Those Requiring a Single Dose				
0- 4.0	50	24	6	9
4.1- 8.0	69	33	15	24
8.1-12.0	5	1	3	4
12.1-16.0	0		4	6
Those Requiring Multiple Doses				
4.1- 8.0	26	12	4	6
8.1-12.0	33	16	4	6
12.1-16.0	10	4	5	8
16.1-20.0	5	1	7	11
20.1+	4	1	13	21
	—	—	—	—
	202	100	61	100

* The remaining 75 patients in the series had either post-thyroidectomy goiters which could not be classified or the thyroid was not palpable.

TABLE 7.—*Comparison of Reports by Various Authors*

Single Doses of I^{131}, Av. Mc.	No. Doses Given, % Euthyroid or Myxedematous				Permanent Myxedema, %	Total Cases	Authors
	1	2	3	4			
11.0-13.0	75.3	20.9	3.0	0.9	20 *	329	Beierwaltes et al.[1]
8.3	59.0	21.0			12	500	Blomfield et al.[5]
8.0 †	56.1	25.5	18.4		11	628	Clark et al.[3]
7.0	46.6			‡	11 ‡	257	Seed et al.[4]
6.4	75.1	9.8	1.7	0.3 §	8	520	Chapman et al.[6]
6.0 ‖	57.3	27.2	11.4	2.0	14.8 ¶	525	Werner et al.[4]
5.5 #	56.6	32.1	9.4	1.8	5.7	106	Bauer et al.[7]
3.0	49.1	30.0	13.3	5.8	2.5	120	Gordon et al.[8]
4.6	60.0	26.0	7.0	11.0	9.1	338	This series

* "Temporary or permanent myxedema," 4%-5% radiation thyroiditis; occasional thyroid storm.

† Calculated from the authors' report, assuming average goiter weight at 40 gm. and average dose of I^{131} at 200 μc. per gram.

‡ Twenty per cent of patients not brought to euthyroid state. Follow-up data obtained from letters and telephone calls.

§ Of series, 0.6% reported "better but toxic"; "occasional thyroiditis"; patients not retreated while improving—in some cases waited six months.

‖ "Average initial dose" quoted by the authors.

¶ During the first year after treatment 7.6% became hypothyroid, but an additional 7.2% manifested myxedema more than one year after therapy.

Calculated from authors' report, assuming average goiter weight at 40 gm., effective half-life of I^{131} at five days, uptake at 50%.

Comment

A precise comparison of the results in this report with data published by other investigators is not possible solely on the basis of their publications. Details which we consider significant are frequently omitted; time intervals between treatments vary from one patient to another. Each series has a different proportion of diffuse and nodular goiters; the average age of patients is different in each group. Table 7 contains data reported by other workers. The results may be cautiously compared with ours.

In the series being compared the average single doses ranged from 11.0 mc. to 3.0 mc., so there can be no denying that some series of patients received almost four times as much radiation as patients in some other series. There is a slight direct relation between the size of the average dose and the number of patients brought to the euthyroid state with a single dose of I^{131}; the largest average dose controlled 75.3% and the least, 49.1%. When the percentages of patients brought to the euthyroid state by both one and two doses is compared, the larger doses show little advantage. Omitting the data of Seed et al. and proceeding from the top to the bottom of Table 7 the patients controlled with both one and two doses were 96.2%, 80%, 81.6%, 87.8%, 84.5%, 88.7%, 84.5%, 79.1%, and 86.0%. The highest average dose apparently produced the most radiation thyroiditis and thyroid storm in saving about 10% of the patients the trouble of receiving a second dose of I^{131}. The range of permanent myxedema in the various series was from 2.5% to 12%; the lower values occurred with the lower average doses. In this category, however, the final figures are greatly dependent upon the length of post-therapeutic observation and the incidence of myxedema may not vary as much as the Table indicates. For example, one gets the impression that the patients in the series of Chapman et al. were followed for very long periods of time, whereas some of ours were not followed for longer than six months before hormone therapy was started.

This comparison leaves us with the conclusion that we would prefer to subject our patients to less radiation with an average dose of 4.6 mc. of I^{131} and achieve control of 86% of the patients with one or two doses of radioiodine rather than increase the average dose and control more patients with one dose, thereby subjecting them to radiation thyroiditis and thyroid storm.

Summary

A series of 338 patients with thyrotoxicosis were treated with average administered doses of 4.6 mc. I^{131} and observed at three-month intervals for at least six months after the euthyroid state had been attained or until permanent myxedema from therapy had been demonstrated. Control of the disease was achieved in 60% of the patients with a single dose and in 86% with one or two doses. The over-all incidence of permanent myxedema was 9.1%. One patient developed thyroid storm during treatment. No instances of radiation thyroiditis were observed. These results compare favorably with those of other series of patients treated with higher average doses of radioiodine.

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Trepopnea

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It is a great and sobering and somewhat paralyzing honor to be asked to deliver the Frank Billings Lecture this year. How great an honor it is was not sufficiently obvious to me until I had looked over the names of the lecturers and the substance of their discourses since Dr. Joseph L. Miller [1] inaugurated the series, in 1930.

I was tempted to give a historical review of Frank Billings and of this lectureship until I found that this had been done to perfection by Dr. William S. Middleton,[2] in 1956, and by Dr. C. Sidney Burwell,[3] in 1957.

So, without a further introduction, I will do what Winston Churchill described himself as doing in his first political address, at Bath. He said, "Hardening my heart, summoning my resolution, I let off my speech."

About twenty-five years ago, Dr. Wolferth and I became interested in a phenomenon and described it in two papers.[4,5] It is obvious that our observations did not reach a large audience. I should like to reintroduce the subject by recounting what seems to me a striking example.

A boy of 17 years had rheumatic mitral and aortic valvular disease, marked cardiac enlargement, and congestive heart failure. After a number of preliminary observations were made, we wished to test the reality of certain of his symptoms. Consequently, on the night of March 17, 1937, we went to his bedside while he was sleeping, lying as he always did on his right side, and we turned him quietly on his left side without waking him. He stayed in that position for 20 seconds; then, without waking, he turned back on his right side. We turned him on his left side a second time. After 15 seconds he turned back on his right, still asleep. A third time we turned him on his left side. This time he slept there for a minute. He then became very dyspneic; sat bolt upright, almost before he was completely awake; breathed hard for half a minute; lay down again on his back; then on his right side, and went to sleep. The next morning he had no recollection of these events. From March 17 to March 30, we asked the nursing staff to record his position each hour during the night. He was never found sleeping on his left side. On the night of March 30 we again went to his bedside, found him sleeping on his right side, and turned him on his left without waking him. He lay there for 30 seconds, then began to cough and breathe hard. Shortly thereafter he awoke and sat up, coughing and breathing heavily for five minutes. He then lay down on his right side and went back to sleep. He remembered *this* episode the next morning. During the first week of April his congestive failure began to subside. By April 24, he was able to sleep on his left side in apparent comfort.

This episode was the culmination of a number of observations, which had begun in the following way: One day in the laboratory, in the early 1930's, we were preparing to occlude a dog's coronary arteries in order to study certain electrocardiographic phenomena. We had opened the chest and the pericardium, and were about to isolate a coronary artery, when the heart slid down to the left into the paraspinal gutter. After

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a brief period it ballooned up, became cyanosed, went into ventricular fibrillation, and the day's experiment came to a premature and exasperating end.

Several nights later I was restless and wakeful, and this event recurred to my mind. I suspected that when the heart had slid to the left, it had kinked an inflow or outflow tract or a coronary vessel. It then occurred to me to wonder whether anything of the sort ever happened in patients with heart disease, particularly in a person with a large heavy heart; whether lying on one side or the other would cause the heart to move and thereby to obstruct an incoming or outgoing vessel and produce symptoms.

The next morning in cardiac clinic I found a patient with a moderate degree of congestive failure, and I asked him about recumbent position preferences for sleeping. He told me he could not sleep on his left side as he became short of breath. I asked him to lie on that side so that I could observe his symptoms. For 15 or 20 seconds he was comfortable in this position; then he began to breathe more deeply, and somewhat irregularly, and complained of shortness of breath and discomfort in the left side of his chest. After a minute or so, I asked him to turn on his right side, his favorite recumbent position. In 10 or 20 seconds he looked relaxed and comfortable once more and announced that his shortness of breath and his discomfort were gone.

This started us off on a long series of observations. We first took a cursory look through the literature and found nothing (later we found a good deal more[5]), except a statement in a patent medicine advertisement in a Philadelphia newspaper: "Don't sleep on left side, affects heart. Right side best." Almost every physician has heard the statement, "It is bad for your heart to lie on the left side." Probably most of us had regarded it as a mere superstition, possibly because left lateral recumbency induces cardiac consciousness in many people. However, our study of the problem suggests that this bit of folklore, like many others, may be based on a modicum of fact. Its incompleteness is illustrated by the story of one of our patients who never realized he had this syndrome until one day a druggist told him it was "bad for the heart" to lie on the left, the only position in which he slept comfortably. That night he lay on his right. Before long he became so weak and short of breath that he could barely attract the attention of his mother in the next room, who came in, turned him over, and revived him. When tested, he proved to be comfortable lying on the left or prone, but developed symptoms when lying on the right or supine.

We satisfied ourselves, as a result of these and many other observations, that certain patients with heart disease who can lie comfortably in one recumbent position, usually the right lateral, cannot tolerate another recumbent position, usually the left lateral, and are forced to abandon the latter for the former by symptoms they cannot endure.

This leads to the question, Is there a similarity of pattern of recumbent-position preference in all persons with this clinical syndrome? We soon found out what you have already guessed from the study of the patient just described—that this is not the case.

Figure 1 shows the various position-perference patterns of 52 patients with trepopnea. Of the entire 52, 33 were most comfortable on the right and 35 were least comfortable on the left, but there were many variations from this pattern. In some patients, a very slight change in position would bring on or relieve symptoms.

So here we had a phenomenon, and, as you might expect, we began casting about for a suitable name. At dinner one evening I described it to a patent lawyer, Mr. John H. Austin, and asked him what he would call it if he wanted to patent it. After some consideration, he said, "Why not call it 'rolling relief'?" Next day I asked Dr. Detlev W. Bronk how to say "rolling

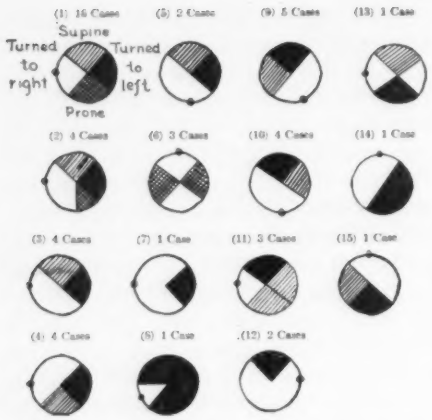

Fig. 1.—The various position-preference patterns of 52 patients with trepopnea. Each diagram shows the entire 360 degrees of possible recumbent position as seen by an observer standing at the foot of the patient's bed. The best position is marked with a small circle. The shaded portions of the circle indicate the positions which are not liked. The most deeply shaded is the most unfavorable position. For instance, the patients depicted by the first diagram in the upper left-hand corner were most comfortable on their right, most uncomfortable on their left, and moderately uncomfortable prone and supine. The 20 cases in Group 4 (trepopnea of necessity) were distributed as follows: (1) nine cases, (2) two cases, (3) one case, (4) two cases (9) four cases, (10) one case, (11) one case. In five cases in (1) and in both the cases in (12) the degree of discomfort lying prone is not known. In (6) one patient was more comfortable on the left than on the right; a second showed the reverse; the third was equally uncomfortable on both sides. Reproduced with permission from Wood, F. C., and Wolferth, C. C.: *American Journal of Medical Sciences* 193:354, 1937; Lea and Febiger, Philadelphia.

relief" in classical language. His solution was "rotopnea." When Dr. Richard A. Kern heard this, he objected on the basis of its being a bastard term, "roto" being Latin and "pnea" being Greek, and he suggested that "roto" should be replaced by the Greek "trepo," to twist or turn (the basis of "treponema"). So "trepopnea" it became and has remained.

Persons can be grouped in four general categories in regard to trepopnea: (1) those who can lie comfortably in any recumbent position; (2) those who prefer one position or who object to another for relatively minor reasons, such as habit or annoyance at hearing or feeling the heart beat; (3) those who have more compelling reasons for preferring one recumbent position to another, who experience dyspnea or discomfort in the chest when in the unfavorable position but who can tolerate it, and (4) those who are actually forced to abandon one recumbent position for another by symptoms they cannot endure. The last two groups constitute the material on which the following observations were based. At first only the patients in Group 4 were studied, but it soon became evident that there was no clear-cut dividing line between Group 3 (*trepopnea of choice*) and Group 4 (*trepopnea of necessity*). Both groups described the same symptoms and exhibited the same behavior. Those in Group 4 either experienced greater discomfort than those in Group 3 or possessed less fortitude, and we were not always able to distinguish between these two possibilities in borderline cases.

In order to study the phenomenon further, we asked ward night nurses to check the positions in which all the patients slept each hour during the night. The results of these observations have been reported in detail[4] but may be summarized as follows: In 40 adults with no cardiac disease, 1,390 observations were made. They were found lying on their left 305 times, on the right 410 times, supine 615 times, and prone 60 times (left, 22%; right, 30%; supine, 44%; prone, 4%). Many of these persons expressed a preference for a certain recumbent position, but their nocturnal behavior showed that their sleeping position pattern was normal.

The nocturnal position patterns of patients with trepopnea differed markedly from the normal.[4] The vast majority of patients with trepopnea of necessity were not found asleep in their unfavorable position at any time. The patients with trepopnea of choice spent much less time than the normal group in their most unfavorable recumbent position.

This study revealed two patients who did not have heart disease and who were never

TABLE 1.—*The Relative Frequency with Which the Various Symptoms Were Outstanding Complaints in an Unfavorable Recumbent Position* *

	Group 3, Trepopnea of Preference	Group 4, Trepopnea of Necessity	Total
Total No. patients	32	20	52
Dyspnea	30	20	50
Precordial discomfort	22	16	38
Palpitation	7	10	17
Fatigue & weakness	5	6	11
Cough	4	6	10
Angina	2 †	1 ‡	3
Nervousness & restlessness	1	2	3
"Heart beating in fingertips"	2	0	2
Dizziness	0	3	3
Epigastric pain	1	1	2
Pain in neck, left shoulder or arms	2	1	3
Fullness in head & feeling of eyes bulging	3	1	4

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† Not observed by us.

‡ Observed by us.

found sleeping on the left side. They both had ulcerative colitis. We pondered for some time as to the reason for their avoiding the left side while sleeping, without coming to any conclusion. Finally we asked one of them, and received the answer, "If I lie on my left side I have to get up and move my bowels." There are probably several other reasons, neither circulatory nor respiratory, why occasional patients may differ from the normal pattern in nocturnal sleeping positions.[4]

The symptoms that induced patients to change from one position to another are shown in Table 1. The most frequent were shortness of breath and discomfort in the region of the heart, but there were many other uncomfortable subjective sensations. These have been described in detail in our first paper,[4] so I will not take the time to do it now.

There was usually a latent period between the time the trepopneic patient assumed his unfavorable position and the onset of symptoms. This varied from 10 seconds to 2 minutes, the average being 20 seconds. The length of time the unfavorable position could be endured varied from 30 seconds to half an hour. The symptoms usually disappeared in 5 to 15 seconds after a favorable recumbent position was resumed. When a few patients remained in an unfavorable position too long they experienced alarmingly severe attacks of dyspnea and sometimes took 10 to 15 minutes to recover, having to sit up to obtain relief.

The respiratory phenomena varied. Some patients breathed more deeply and more rapidly. Others showed obvious evidences of anxiety and discomfort, but their respiratory rate or depth did not seem to increase. Thus far our studies have shown no reduction of vital capacity shortly after a patient with trepopnea assumes his unfavorable position. It was difficult to evaluate the vital capacity after dyspnea supervened.

As is well known, mitral systolic and diastolic murmurs usually become louder when the patient lies on the left side. Rate and rhythm of the heart showed no consistent change, except that a certain number

TABLE 2.—*Cardiovascular Characteristics of 52 Patients with Trepopnea* *

Etiology	Group 4	Group 3	Total
Rheumatic	9	15	24
Degenerative	7	13 †	20
Syphilitic	2	3	5
Congenital	1	0	1
Subacute bacterial endocarditis	1	0	1
Unknown	0	1	1
Total	20	32	52
Enlargement of heart			
Unknown	0	1	1
Slight	2	3	5
Moderate	5	15	20
Marked	5	11	16
Very marked	8	2	10
Total	20	32	52
Functional classification			
Class I	0	0	0
Class II-A	0	3	3
Class II-A to B	8	14	22
Class II-B	3	7	10
Class III	9	8	17
Total	20	32	52

* Reproduced with permission from Wood, F. C., and Wolferth, C. C.: *American Journal of Medical Sciences* 193:354, 1937; Lea & Febiger, Philadelphia.

† Two of these were moderately thyrotoxic.

of patients had more premature beats in their unfavorable recumbent position. No changes, consistently related to trepopnea, were observed by us in the arterial blood pressure, venous pressure, or the electrocardiogram. However, our studies in this regard are incomplete.

The nature and manifestations of the heart disease in our 52 trepopneic patients are shown in Table 2. You will see that the etiology is variable but that most of the patients had cardiac enlargement and a considerable degree of functional impairment of the heart. Yet there were many other patients with serious cardiac impairment who did *not* experience trepopnea.

To follow up our original suspicion that movement of the heart was responsible for trepopnea, we studied fluoroscopically the mobility of the heart that resulted as the subject first lay on one side, then stood upright, and then lay on the other side. Measurements were made in normal persons, in patients with heart disease without trepopnea, and in persons with trepopnea. No facts were uncovered that helped to explain the mechanism. As a patient moved from the right lateral decubitus to the left or vice versa, the distance the heart moved did not seem to be related to the presence or absence of trepopnea. The most marked cardiac movement we saw is shown in Figure 2. This patient had trepopnea of choice. He preferred lying on the right. Lying on the left was his most uncomfortable position. The heart moved all the way from one chest wall to the other when he turned over.

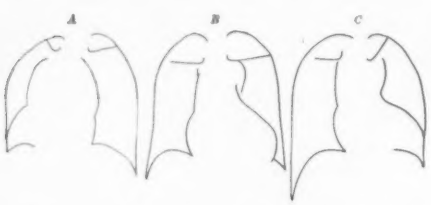

Fig. 2.—Orthodiagrams of a patient with degenerative heart disease and trepopnea of choice, showing marked movement of the heart and definite change in shape of the supracardiac shadow, with change of position. *A*, patient lying on right (best position). Heart against the right chest wall. Supracardiac shadow 11 cm. in width. *B*, patient erect. Supracardiac shadow 7.5 cm. in width. *C*, patient lying on the left (worst position). The heart has moved 6.5 cm. to the left, when compared to *A* and is now resting on the left chest wall. The supracardiac shadow is 7.8 cm. in width. The movement of the heart in this patient was about as great as any we have seen. Reproduced with permission from Wood, F. C., and Wolferth, C. C.: *American Journal of Medical Sciences* 193:354, 1937; Lea & Febiger, Philadelphia.

Very naturally, after making these observations, we believed that we had discovered *the* cause of paroxysmal nocturnal dyspnea, i.e., the person with trepopnea, while asleep, rolls on his bad side and wakes up with acute dyspnea and cough. Consequently, we made observations on 33 patients from this point of view[5] and were convinced that in a number of persons trepopnea *was* an etiological factor in paroxysmal dyspnea. However, many patients with trepopnea did not give a history of waking short of breath at night. Possibly they had the ability to avoid their unfavorable position during sleep, like the patient described at the beginning of this paper whose slumbers were disturbed by our curiosity. Moreover, in some patients with a history of paroxysmal dyspnea, trepopnea could not be demonstrated while they were awake. Thus we concluded that, although trepopnea *was* a factor in many instances, it was not necessarily the *one and only* cause of paroxysmal nocturnal dyspnea.

One patient led us down another path of thought. She was a 59-year-old woman with rheumatic heart disease, mitral stenosis, atrial fibrillation, and marked cardiac enlargement. She suffered a left hemiplegia, presumably from a cerebral embolus, and became semistuporous. In an attempt to prevent hypostatic pneumonia, the nurses had been ordered to turn her from side to side periodically. After a number of alarming "heart attacks" it became clear to her physician that a "heart attack," with rapid pulse, cyanosis, and a frightening change in her general appearance, occurred each time she was turned on her left side.

This and other observations led us to wonder what would happen to a patient with trepopnea who was narcotized or anesthetized and turned to an unfavorable recumbent position that she was obviously powerless to change.

At about this time my own active study of trepopnea was interrupted by World War II and has not been resumed. Consequently, from this point on, the observations have been assembled by a process that Dr. George P. Müller used to call "bird nesting," which he defined as collecting the observations and productions of others for the support of one's own hypothetical eggs and incidentally for the support of one's wife and family.

I have talked frequently concerning trepopnea with Dr. Robert D. Dripps, Dr. James E. Eckenhoff, Dr. Henry L. Price, and others in our Department of Anesthesia. They are acutely aware of the potential danger of certain recumbent positions to patients with serious heart disease who are under anesthesia. They have not as yet made any controlled studies, but they have witnessed a number of dramatic incidents, such as the following:

On June 6, 1958, a woman had a mitral valvulotomy while lying on the right side. The operation was completed satisfactorily with a blood loss of 400 cc., of which 300 cc. had been replaced. The patient was recovering from the anesthetic and had opened her eyes. She was turned flat on her back at 9:35 a.m. and suffered cardiac arrest. She was turned on the right side again but did not recover. The chest was opened at 9:47; the heart was not beating; it was massaged; it went into ventricular fibrillation and could not be resuscitated. Autopsy disclosed no obvious cause of this sudden cardiac arrest.

The anesthesiologists also tell me that patients with mitral stenosis and fairly severe congestive failure, when under anesthesia, often cannot be placed in the right lateral position without a dramatic fall of blood pressure. In such persons the operation must be done with the patient supine and with the head of the table raised.

Lurie[6] wrote us of a ". . . vivid recollection of paroxysmal tachycardia occurring at the moment of clamping a patent ductus with the patient in the right lateral decubitus. . . . Various drugs were used unsuccessfully in an attempt to arrest the arrhythmia. When the chest was closed and the patient placed on his back, regular sinus rhythm was resumed in a matter of seconds."

These isolated reports prove nothing; however, our anesthesiologists are acutely aware of the potential danger of turning an anesthetized patient with serious heart disease from one recumbent position to another. Moreover, when they obtain any preanesthetic evidence or hint of trepopnea, they respect it during anesthesia. It is their clinical impression that they cannot predict, as a result of preoperative study, which patient will be unable to tolerate a certain recumbent position during anesthesia.

Of course, we have wondered why the anesthesiologists have not observed more difficulty from the left lateral position and why they could not predict trouble by preoperative study. On further questioning, it developed that they were primarily concerned with hypotension rather than with dyspnea and that their preoperative observations were largely based on blood pressure measurements in certain recumbent positions, which we had not noted to change in studying our trepopneic patients. They have made the following observations:

1. Certain patients, preparatory to nephrectomy, when placed on the side and jack-knifed over a sandbag, may experience dramatic hypotensive episodes, which are relieved promptly by removing the sandbag.

2. Certain pregnant patients at term may develop marked hypotension when they assume the supine position.

3. Any recumbent position change in an anesthetized patient is potentially a producer of acute hypotension.

Thus we suspect that the positions that give anesthesiologists the most trouble are

those which produce a dramatic interference with venous return to the right side of the heart, most often by obstruction of the inferior vena cava.

Further study may show that certain of the symptoms we encountered infrequently, such as weakness, dizziness, restlessness and fullness in the head, and feeling the eyes bulging, are accompanied by falls in blood pressure and are produced by vena caval obstruction. It may be that there are relatively few trepopneic patients who develop real pulmonary edema in their unfavorable recumbent position and that the anesthesiologists are not troubled by minor degrees of "dyspnea." It is even possible that anesthesia may have the effect of mitigating certain respiratory reflexes related to dyspnea. Further observations are required to explain some of these discrepancies.

After writing the foregoing paragraph, I ran across the following patient in a cardiac seminar on April 30, 1959. A man of 33 was operated on the day before, in the right lateral position, for mitral stenosis. When his chest was opened, the anesthesiologist noted that the lungs seemed to be stiff and difficult to inflate. About 15 minutes after the mitral valve was opened the patient developed ventricular fibrillation, which was terminated by several electric shocks. The patient recovered but died suddenly on the 12th day. Necropsy showed no obvious cause of death, and ventricular fibrillation was suspected.

When I called this patient to Dr. Dripps' attention, he was very much interested. He said it was a relatively uncommon occurrence, which he had in the past attributed to bronchospasm. However, it might be exactly what we were looking for in that it might be related to trepopnea: pulmonary venous obstruction with pooling of blood in the lungs could produce the phenomenon.

Several other observations concerning the relations of position to cardiorespiratory function will be recorded in the hope that they will serve as parts of a jigsaw puzzle that in the future someone will put together to make a complete picture.

(*a.*) Schnabel et al.[7] reported a patient who, after right pneumonectomy for carcinoma, developed severe anginal pain, dyspnea, and cyanosis while standing or sitting, which were relieved completely by lying down. The arterial oxygen saturation was "definitely and consistently higher when the patient lay on the right side than on the left." These symptoms and signs were cured when an atrial septal defect was discovered and repaired surgically. Since then, Kirby[8] has had another patient identical in every respect to the one just mentioned.

(*b.*) In 1784, William Hunter[9] reported an 8-year-old cyanotic child with the tetralogy of Fallot, whose most distressing symptoms were fits. "Any hurry upon his spirits or brisk motion of his body would generally occasion a fit. And for some of the last years of his life he had found out, by his own observation, that, when a fit was coming upon him, he could escape it altogether, or at least take considerably from its violence, or duration, by instantly lying down upon the carpet, on his left side, and remaining immoveable in that position for about ten miutes. I saw the experiment made with success." In 1953, Lurie,[10] who called my attention to William Hunter's report, demonstrated that in patients with the tetralogy of Fallot a reduction in venous return tended to bring on attacks of cyanosis and dyspnea and that the various positions that these patients liked to assume to relieve their symptoms improved the venous return to the heart. He reports that orthopnea is conspicuous by its absence in the tetralogy of Fallot, as well as in other types of congenital heart disease characterized by a combination of (1) a reduction of pulmonary blood flow, (2) a venoarterial shunt, and (3) a high systemic blood flow.

(*c.*) Corcoran[11] noted "orthostatic dyspnea" in hypertensive patients receiving hexamethonium, i.e., they were dyspneic standing and not while lying down (re-

duced venous return through the inferior vena cava?).

(*d.*) A remarkable orthopnea was reported in a patient with partial paralysis of the muscles of respiration,[12] who had no heart disease.

(*e.*) Patients with artificial pneumothorax are uncomfortable lying on the side of the pneumothorax.

(*f.*) Patients with asthma or with pulmonary fibrosis and dyspnea seem to be less likely to show orthopnea and trepopnea than patients with congestive heart failure.

(*g.*) The remarkable position preferences of certain patients with pericardial effusion are well known.

It is our suspicion that orthopnea and trepopnea are related. They both seem to occur in patients with pulmonary congestion. Both seem to subside when congestive failure clears. Both are sometimes exaggerated by extension of the neck and mitigated by its flexion. Many trepopneic patients can lie flat on the right side but need several pillows to enable them to lie on the left. Consequently, when the mechanism of production of trepopnea is discovered, it may throw some light on the cause of orthopnea. We also suspect that studies such as those made recently concerning orthopnea by Sharp and his co-workers [13] will show that a trepopneic patient, with dyspnea as his chief symptom, suffers a similar reduction of lung compliance in his unfavorable recumbent position.

Summary

Certain cardiac patients can lie comfortably in one recumbent position and cannot tolerate another.

Patients rarely volunteer this information to a physician. This probably accounts for the fact that the phenomenon of trepopnea has not become generally recognized.

Anyone who looks for trepopnea will find many examples of it, mild and moderate in degree more frequently than severe.

The mechanism of production of trepopnea has not been worked out. At the moment our best guess might be outlined as follows: Pulmonary congestion from cardiac failure provides the background. When a patient rolls to his unfavorable position, the heart sags to that side, obstructs pulmonary venous return and further increases pulmonary congestion, thereby producing dyspnea. Other symptoms of trepopnea may be due to other mechanisms. The final proof or disproof of these speculations may well come from studies with cardiac catheters and from modern methods of measuring respiratory functions.

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Current Clinical Status of Lipid-Mobilizer Hormone

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A number of studies dealing with a lipid-mobilizing hormone (LM) have been reported from these experimental and clinical laboratories.[1-18] This substance was discovered, in 1954, by Seifter and Baeder.[1] These investigators, working with rats and dogs, demonstrated a lipemia-clearing effect with hyaluronidase, with hyaluronate, and with deoxycorticosterone. At the same time, they found that the lipemia-clearing effect of these substances could be inhibited by the administration of cortisone or by stress (cold exposure) and by nephrosis. Studies in connection with the latter findings led to the discovery of LM in the plasma of several animal species, including man.[2] Other experiments by Seifter and Baeder revealed that the pituitary was essential for the release of LM.[3] More recently, LM was recovered from the posterior pituitary of hogs,[4] denoting that this hormone is either produced or stored at that site. LM is dialyzable; it has been crystallized and appears to be an octapeptide.[7] LM is effective when administered parenterally but not when given via the oral route. The primary action of LM, as will become evident, is that of mobilization of triglycerides from the omental and mesenteric depots.

The purpose of this report is to summarize our observations on the effects of this hormone in man. First, some results of the administration of exogenous LM will be indicated, and then certain findings regarding the actions of endogenous LM will be presented. In addition, attention will be drawn to studies which show that the oral administration of a partially depolymerized hyaluronic acid will inhibit the response to LM.

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Professor of Clinical and Research Medicine (Dr. Zarafonetis); Director, Wyeth Institute for Medical Research (Dr. Seifter); Pharmacologist, Wyeth Institute for Medical Research (Dr. Baeder), and Research Fellow in Medicine (Dr. Kalas).

I. Exogenous LM

A. Effects of Single Injection.—With regard to exogenous LM, dialyzates and crystalline material were prepared from the plasma of cortisone-treated horses. The LM activity of plasma from an animal so treated was about 1,000 times that found in the plasma of an untreated, nonstressed animal.[2] From Figure 1 it can be seen that the injection of only 1.2μg. of the crystalline

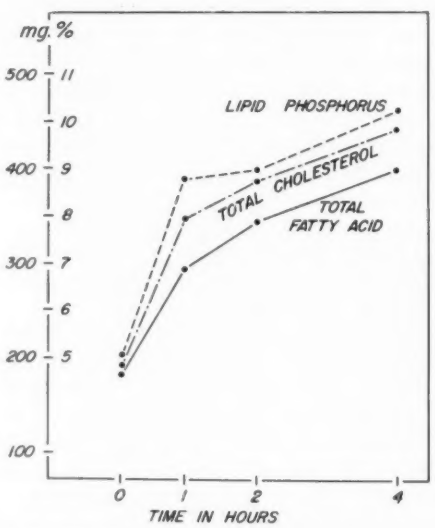

Fig. 1.—Plasma lipid response to intravenous injection of 1.2μg. of crystalline LM hormone in fasting 46-year-old Negro man, weight 83 kg.

material into a fasting convalescent patient was followed by a prompt and marked increase of the plasma lipids. The depicted results are comparable to those observed in other fasting patients who were given injections of either crystalline material or plasma dialyzates containing LM. Although most of the subjects tested characteristically exhibited a rise in cholesterol, lipid phosphorus, and fatty acid values after administration of LM,[4,5] an occasional patient showed a significant rise only of the fatty acid component of the plasma lipids (Fig. 2).

B. Effects of Multiple Injections.—In view of the striking responses achieved with single injections, studies were undertaken to determine the effects of repeated injections of LM. Accordingly, LM was administered daily for two weeks to four patients who were maintained on a diet which provided only 4.8 gm. of fat daily.[8] In all of these subjects, there resulted a remarkable elevation of plasma cholesterol, fatty acids, and lipid phosphorus, which was sustained as long as the injections were continued. Although there was also a concomitant increase in fecal and urinary cholesterol excretion, the amounts involved accounted only for a fraction of that mobilized. There was no evidence that LM enhanced the metabolism of lipids which were mobilized by it.

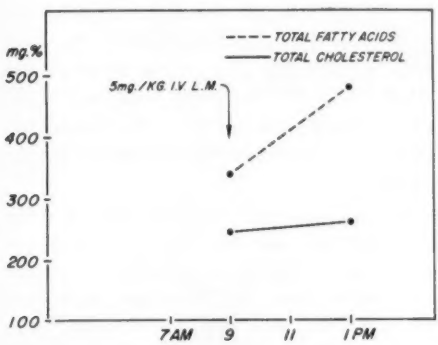

Fig. 2.—Plasma lipid values in patient, 33-year-old Negro woman, before and four hours after the intravenous injection of 220 mg. of LM dialyzate. In this instance, the principal change was in the fatty acid component.

When LM was administered in a similar fashion to two other patients on a high-fat diet, the hyperlipemic response was not observed.

These observations indicated that an appropriate metabolic posture was necessary for the lipid-mobilizing effect of LM to be elicited or manifest or both.[8]

C. Effects of Prefeeding.—Since nonfasting patients and subjects on a high-fat diet did not respond to intravenous injections of LM, it was reasoned that the blocking effect of prefeeding might be due to a specific food class rather than to caloric intake alone. Accordingly, the effect that prefeeding with a meal of carbohydrate, fat, or protein might have on the acute response to LM was investigated.[12] Meals of glucose or cream but not of amino acids were found to block the hyperlipemic effect of LM.

The metabolic basis for the foregoing observations is not entirely clear. However, some experimental studies by Seifter and Baeder [9,11] and clinical studies to be cited below appear to bear directly on certain of these findings.

Seifter and Baeder [9] found that injections of LM into animals were uniformly followed by mobilization of triglycerides from the mesenteric depots to the liver. Whether or not there followed hyperlipemia of the peripheral blood depended on the capability of the liver to cope with the lipid load presented to it. Moreover, certain factors which influenced the ability of the liver to metabolize the mobilized lipids were determined. Adequate stores of glycogen, for example, would permit the liver to retain and metabolize the mobilized triglycerides, whereas severe depletion of glycogen modified liver lipid metabolism, with resultant peripheral lipemia. In addition, exposure to minute amounts of potentially hepatotoxic agents would sensitize animals to the effects of LM. Thus, it became apparent that in animals the liver played a key role in the manifest response to intravenous injections of LM, as it must also to endogenous LM released under situations of stress.

It should be noted further that the uniform peripheral hyperlipemia elicited by LM administration in the subjects tested in the various studies described herein implies adequate liver glycogen depletion either through prior fasting or by virtue of hepatic derangement through disease or other factors, in addition to the period of fasting.

II. Endogenous LM

A. Effects of Surgical Stress.—With the preceding studies available as background, it was of obvious importance to determine whether the observations made in experimental animals were also applicable to man under conditions of acute stress. Accordingly, the effect of surgical stress on the plasma concentration of lipid-mobilizer hormone and on the plasma lipids was investigated in a series of patients.[10,16]

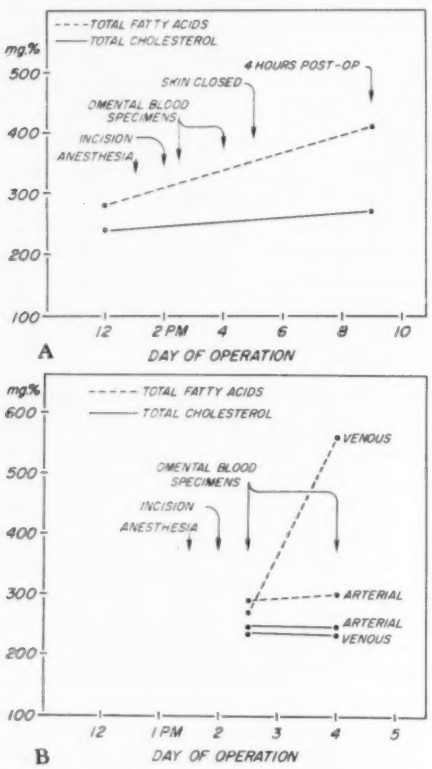

Fig. 3.—*A*, plasma lipid values (antecubital vein blood) of patient, 33-year-old Negro woman, before and after cholecystectomy. Note the relatively small postoperation increase of peripheral lipid values despite the sharp rise in omental vein fatty acids as shown in *B*. *B*, plasma lipid values of omental artery and omental vein blood specimens taken at indicated times from patient during cholecystectomy. Note the marked increase of fatty acids in prehepatic blood obtained from the omental vein late in surgery over the levels found in the baseline specimens and in omental arterial blood taken at the same time.

Blood specimens were collected from the antecubital vein before and four hours after operation and from branches of the omental artery and omental vein at the beginning and at the end of intra-abdominal operative procedures. These samples were analyzed for plasma cholesterol and total fatty acids and were assayed for lipid-mobilizer hormone activity by in vivo or in vitro methods or both.[15,16] In addition, paper electrophoretic analysis of the plasma proteins and lipoproteins of these specimens was performed.

Figure 3 gives the plasma lipid values obtained in a patient before, during, and after cholecystectomy. It may be seen that four hours after operation, the plasma cholesterol had increased 30 mg. and the fatty acids 122 mg. per 100 ml., respectively, over the presurgery values. (These changes are roughly comparable to those seen in Figure 2, which depicts the response of the same patient to 5 mg. per kilogram of lipid-mobilizer dialyzate administered intravenously.) Figure 3*B* illustrates the results of the tests on the omental arterial and venous specimens. There is a striking rise in the fatty acids (+288 mg. %) of the omental vein blood taken late in surgery but with little change on the arterial side. The increase in fatty acids, therefore, is contributed by the omentum.

For a group of 11 other patients, the postoperation increase of cholesterol in the peripheral blood averaged 26% over the preoperative level, while the fatty acids rose by 41%. The most striking finding, however, was the marked elevation of total fatty acids in the omental vein blood drawn just before abdominal closure. This increase averaged 122% over the early surgery

values. That the fatty acids were contributed by the omentum was evident from the fact that the arteriovenous difference in the late surgery omental specimens averaged 221 mg. per 100 ml., with a range of from +80 to +526 mg.[16]

The paper electrophoretic studies revealed no significant change of the peripheral and omental plasma proteins during the course of surgery. On the other hand, there was a striking shift from α-lipoprotein to β-lipoprotein predominance in the electrophorograms of omental vein blood during this same period. In some instances, there appeared to be a "spilling over" into the peripheral blood of β-lipoproteins which had been presented to the liver.[16]

Generally, the LM hormone assays of the preoperation and early operation blood specimens were negative, while tests on the late surgery and postoperation blood samples were positive for increased amounts of circulating LM. It was concluded, therefore, that the over-all stresses which are inherent in operations led to the release of lipid-mobilizer hormone during the course of surgery in these patients.

From the foregoing and related observations the following physiologic mechanism for the acute mobilization of lipids to the liver was delineated (Fig. 4).[16]

1. Stress, such as surgery, may stimulate the anterior pituitary to discharge corticotropin (ACTH) into the circulation.

2. The adrenal cortex responds by discharging glucocorticoids.

3. These, in turn, lead to the release of LM from the posterior pituitary.

4. LM acts on the omental (and presumably the mesenteric) fat depot to release neutral fats into the portal circulation. Paper electrophorograms show a marked shift from α-lipoprotein to β-lipoprotein predominance in the omental vein blood at this time. The omentum, therefore, plays an important and dynamic role in lipid metabolism.

Moreover, it should be evident that any lipid changes which may appear in the pheripheral blood during acute stress reflect the foregoing events as well as the

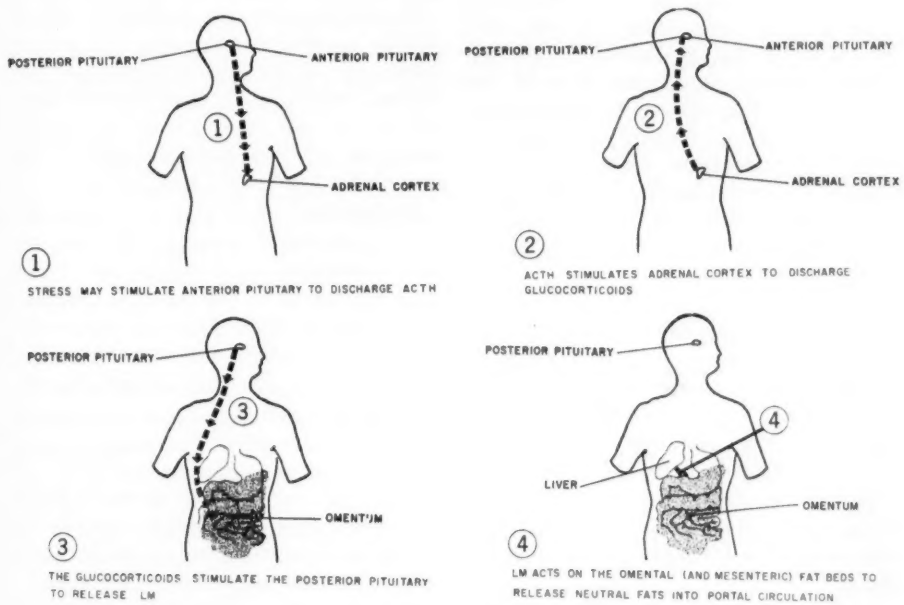

Fig. 4.—Schematic representation of the relationship of lipid mobilizer hormone to stress and caloric needs.

capability of the liver to metabolize the lipids presented to it.

B. Relation to Increased Plasma Lipids of Pregnancy.—Studies [10,14] were also undertaken to determine the possible role of this lipid-mobilizer hormone in connection with the known increase of plasma cholesterol during pregnancy.

Plasma cholesterol and fatty acid determinations were made on blood obtained from the mother during pregnancy, at the time of delivery, and post partum. Similar tests were performed on cord blood and femoral vein blood from the newborn infant. Assays of the LM activity of all of these specimens were also carried out.

The findings may be summarized as follows: The elevation of plasma cholesterol and fatty acids during the course of pregnancy was confirmed. Cord and newborn infant bloods held one-third or less the amount of lipids found in the respective maternal blood obtained at the time of delivery.

Increased plasma LM activity was found to be present during the second and third trimesters and, occasionally, in the first trimester. The rise in plasma LM concentration appeared to antecede that of the plasma lipids. Increased LM activity was uniformly detected in cord and newborn infant blood specimens, as well as in the respective maternal bloods obtained at parturition. Thus, in contrast to the plasma lipids, LM appears to traverse the placental barrier.

These findings suggest that omental and possibly other lipid depots of infants are either depleted prior to birth or do not have an opportunity to accumulate during gestation. Necropsy experience indicates that the omentum is thin and translucent at birth, which is consistent with either interpretation.

Within a month or so post partum, the plasma LM activity and plasma lipids had declined to normal levels in the mothers tested.

C. Relation to Familial Hyperlipemic States.—A number of persons with familial lipid dyscrasias have been tested for plasma lipid-mobilizer activity as well as for the concentration of their plasma lipids.[10] It has been found that these subjects carry, apparently at all times, a very definitely increased amount of circulating lipid-mobilizer hormone over that found in the plasma of nonstressed normal persons.

As yet it has not been possible to determine whether these patients have primary or secondary "hyper-LM-ism."

III. Blocking of Lipid Mobilizing Effect of LM by Partially Depolymerized Hyaluronic Acid (PDHA)

The foregoing studies indicated a striking role of the LM hormone in the normal dynamics of lipid mobilization. At the same time it became evident that derangements of this mechanism may have important clinical implications. Accordingly, considerable attention has been devoted to the development of means whereby the activity of LM may be counteracted or blocked. One of the most promising approaches in this regard has been through the use of PDHA, a partially depolymerized hyaluronic acid. It will be recalled that this was one of the substances which was demonstrated by Seifter and Baeder [1] to cause lipemia-clearing in rats and dogs. The following will summarize our experience in pilot clinical tests so far performed with PDHA.

A. Inhibition of Response to Exogenous LM.—In Figure 5 it can be seen that the oral administration of 3.0 gm. of PDHA prior to injection of LM dialyzate abolished the peripheral lipid response which had previously been elicited with the same amount of LM in the same subject (Fig. 2).

B. Inhibition of Response to Endogenous LM.—1. Acute: PDHA was administered orally in doses of from 400 to 3,000 mg. to nine patients prior to intra-abdominal surgery.[10] Although increased amounts of LM were released into the circulation of all of these patients during the course of operation, lipid mobilization from the omental depot did not ensue. In addition, lipoprotein

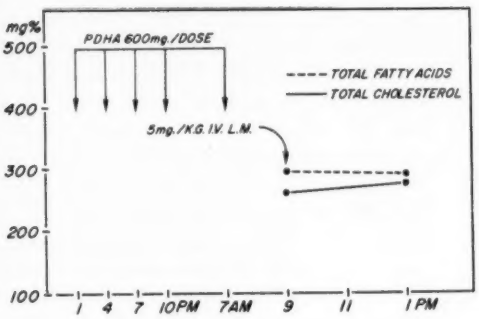

Fig. 5.—Plasma lipid values in patient, 33-year-old Negro woman, pretreated with 3.0 gm. of partially depolymerized hyaluronic acid and then challenged with same amount of lipid mobilizer hormone dialyzate as before (Figure 2). The PDHA appears to have blocked the fatty acid response.

patterns of the prehepatic blood specimens showed no significant change during surgery. This was in contrast to the characteristic shift from α-lipoprotein to β-lipoprotein predominance which occurred in patients who had not been pretreated with PDHA. Thus, PDHA did not prevent the release of LM from the posterior pituitary but did prevent the action of LM at the omental level. In Figure 6 is shown the plasma lipid values of a patient who was given 3.0 gm. of PDHA orally before splenectomy. It can be seen that there was no increase of the plasma lipids in blood collected from prehepatic or peripheral sites. This is in sharp contrast to the blood lipid changes which were noted in the same patient when she later underwent cholecystectomy without pretreatment with PDHA (Fig. 3).

2. Chronic: Since PDHA was found to inhibit the acute response to exogenous LM, studies have been undertaken to determine the effect that long-term administration of this material may have in patients with familial lipid dyscrasias, who, as it has been noted above, carry continuously increased amounts of LM in their plasma.

Results of PDHA administration to a 49-year-old patient and her 16-year-old daughter, both exhibiting features of familial hypercholesterolemia, are shown in Figures 7 and 8. These subjects received PDHA, one 200 mg. capsule a half hour before each meal, that is, 600 mg. daily. There was no dietary restriction during the period of therapy which lasted 85 days in each case. Both patients experienced striking reductions in plasma fatty acids and cholesterol during the period of PDHA administration. There was a prompt rise of the plasma lipids,

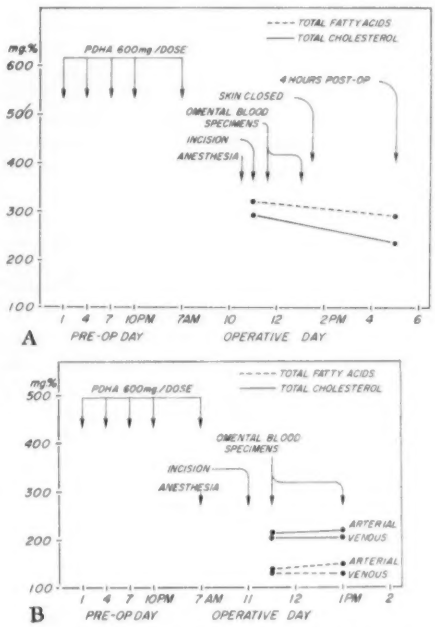

Fig. 6.—*A*, plasma lipid values (antecubital vein blood) of patient, 33-year-old Negro woman, before and after splenectomy. On the occasion of this operation she had been given 3.0 gm. of PDHA, orally, during the preceding 17 hours. Note the decline in the post operation lipid values. (Contrast with Figure 3*A*). *B*, plasma lipid values of omental artery and omental vein blood specimens taken at indicated times from same patient. Note the lack of increase of the fatty acids in the prehepatic blood obtained from the omental vein late in surgery. This is in sharp contrast to the marked increase in plasma fatty acids experienced by the same patient during cholecystectomy but without PDHA pretreatment (Figure 3*B*).

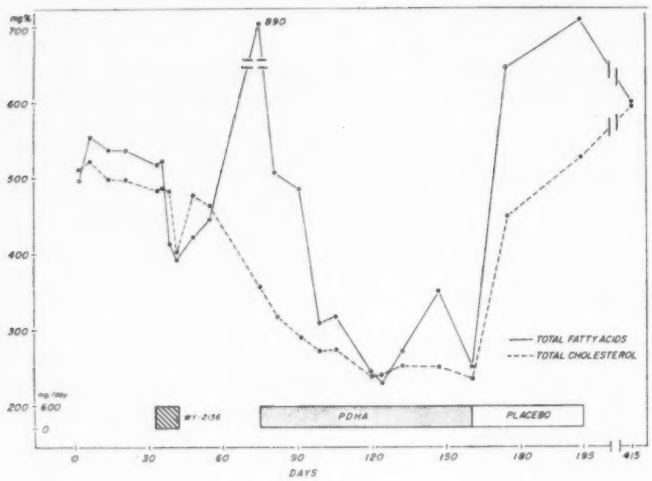

Fig. 7.—Fasting plasma lipid values of patient, a 49-year-old white woman with hypercholesterolemia, before, during, and after 85 days of oral PDHA administration.

however, when a placebo was substituted for PDHA. Assays for the lipid-mobilizer hormone remained strongly positive, whether the patients were on PDHA therapy or not and whether the plasma lipid values were high or low. Neither of these or any other patients who have so far received PDHA have exhibited untoward effects from the compound. It is to be stressed that the study of PDHA in chronic lipemic states is in a preliminary phase and that conclusions regarding its long-term implications are not warranted at this time.

Summary

In summary, the clinical and pertinent animal studies in connection with lipid-mobilizer hormone have been reviewed. The findings have led to the delineation of a physiologic mechanism in man for the acute mobilization of lipids from the omentum to the liver. In addition, the capability of a partially depolymerized hyaluronic acid (PDHA) to inhibit the response to LM has been described.

It is believed that these observations with LM hormone may be of further significance

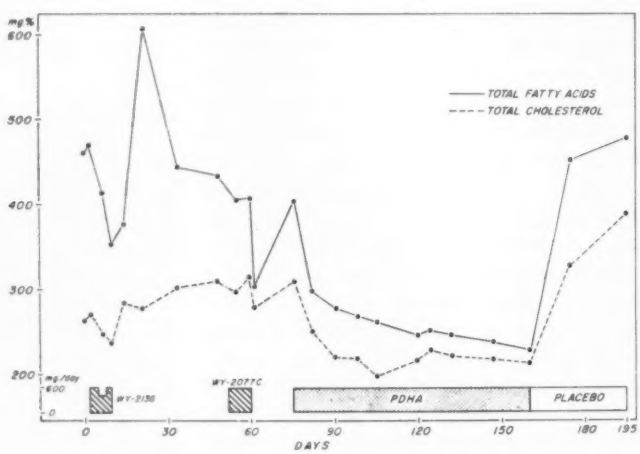

Fig. 8.—Fasting plasma lipid values of patient, the 16-year-old daughter of patient in Figure 7. Note response of plasma lipids to oral administration of 600 mg. daily of PDHA.

in that they provide a means whereby much heretofore unrelated data can be integrated into a picture that is physiologically meaningful. For example, in such superficially diverse states as post-traumatic "fat embolism," hereditary hypercholesterolemia, hereditary hyperlipemia, pregnancy, and nephrosis,[10] it appears that the hyperlipemic component of each is mediated through the lipid-mobilizer hormone pathway.

Similarly, the finding that the action of LM is inhibited by the oral administration of a partially depolymerized hyaluronic acid may have evident therapeutic value. It is hoped, however, that PDHA also has heuristic implications beyond its effect on the dynamics of lipid metabolism as described herein.

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Studies in Man on Hyper- and Hypoaldosteronism

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Introduction

The classification of clinical disorders associated with an abnormal secretion of aldosterone was clearly outlined by Conn.[1] Primary hyperaldosteronism had been previously described by Conn[2] and secondary hyperaldosteronism in patients with nephrosis, congestive heart failure, and cirrhosis by Deming, Luetscher, and Curtis.[3,4] Although the syndrome of primary hypoaldosteronism had not been described, it was anticipated by Conn,[1] and subsequently two patients have been reported as representing examples of this syndrome.[5,6] The exact pathophysiology of primary hypoaldosteronism is still in doubt.[7]

Although increased aldosterone secretion is not necessarily the primary cause of sodium and water retention in patients with edema, it is, in general, one constant finding in the chain of events leading to edema formation. Two groups of substances have been used to modify this aspect of edema; inhibitors of adrenal cortical activity[8] and peripheral antagonists of aldosterone.[9] The therapeutic usefulness of the adrenal inhibitor used most extensively, Amphenone B(3,3-bis[*p*-aminophenyl]-2-butanone), has been limited by undesirable effects, such as anorexia, nausea, vomiting, and sedation.[10] These effects appear to be correlated with the total daily dose and duration of treatment.

The present report will describe studies designed to assess the toxic and metabolic effects of small amounts of Amphenone administered intravenously to a series of patients with secondary hyperaldosteronism. In addition, studies will be reported on two additional patients, one with primary hyperaldosteronism resulting from bilateral adrenal hyperplasia and one whose findings suggest primary hypoaldosteronism. These investigations will be compared with similar studies made on normal subjects.

Materials and Methods

The patients were studied on the medical wards of the University Hospital or Birmingham Veterans Administration Hospital. All of the five patients with secondary hyperaldosteronism resulting from either cirrhosis of the liver, Kimmelstiel-Wilson syndrome, or congestive heart failure had marked edema which was refractory to the usual diuretic regimen. These patients were critically ill, and four of them later died from their primary disease. The daily sodium intake in these patients was maintained at 30 mEq. or less. Amphenone* sterile powder, 1 gm., was dissolved in 1,000 ml. of 5% dextrose in water and administered intravenously over an 8- to 12-hour period during the day. Supplementary Amphenone tablets in doses of 0.5 gm. were given orally at 10 p.m. and 4 a.m. All intravenous infusions were started about 8 a.m. All urine samples were collected from 7 a.m.

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* Drs. E. W. Young and C. J. O'Donovan, Medical Division, The Upjohn Company, supplied the Amphenone used in these studies. The material was supplied in two forms: (1) Amphenone sterile powder, 1.0 gm. per vial, and (2) Amphenone tablets, 0.5 gm. per tablet.

to 7 a.m. and kept refrigerated without preservative.

Urinary aldosterone levels were determined by a modification of the chemical procedure of Nowaczynski, Koiw, and Genest.[11] In this procedure continuous hydrolysis and extraction of the total 24-hour urine specimen at pH 1 for 48 hours is followed by purification on one column and three paper chromatographic systems. Final quantitation is carried out by use of the blue tetrazolium color reaction. Results are expressed as micrograms excreted per 24 hours, with use of hydrocortisone as a standard. With use of this method in our laboratory, values have ranged from 2.3μg. to 13.6μg. per 24 hours, with a mean of 6.4μg., for normal subjects on a free diet.

Creatinine excretion was measured by the method of Clark and Thompson.[12] The urinary 17-ketosteroids were extracted by the method of Drekter et al.,[13] and the colorimetry was performed as in the procedure of Holtorff and Koch,[14] with our own modification of diluting with butanol instead of ethanol for the final colorimetric determination. Results are averages of duplicate or triplicate determinations and are expressed as milligrams of epi-isoandrosterone excreted per 24 hours. With the use of this method in our laboratory, normal values for males have ranged from 8 to 24, with a mean of 15, mg. per 24 hours. The 17-hydroxycorticosteroids were determined by a modification[15] of the method of Reddy.[16] The results are averages of duplicate or triplicate determinations, and are expressed as milligrams of hydrocortisone excreted per 24 hours. Normal values for males in our laboratory have ranged from 1 to 11, with a mean of 5, mg. per 24 hours. Sodium and potassium levels in serum and urine were measured by the flame photometer.

In order to eliminate the effects of minor inaccuracies in the timing of urine collections, each patient's urine values were corrected according to the average creatinine content of all of his specimens. In all cases the corrections were small, and where the creatinine levels were so low as to indicate obviously faulty collections, the values were discarded. Ammonia levels were determined by Conway's microdiffusion technique.[17]

Observations

Secondary Hyperaldosteronism.—Nephrotic Syndrome: Patient 1, a 35-year-old man had had diabetes mellitus for 12 years, which had been poorly controlled with diet and insulin. For 12 months he had had diabetic retinopathy with blurred vision, hypertension, and the nephrotic syndrome. On two occasions a marked exacerbation of his nephrotic syndrome with severe edema necessitated hospitalization and the institution of an intensive diuretic regimen which resulted in a remission on both occasions. His third nephrotic exacerbation was characterized by massive anasarca, bilateral papilledema, stupor, and convulsions. A similar vigorous diuretic and antihypertensive regimen was begun and continued for four days. Because of a gradual deterioration of his condition, Amphenone was begun and continued for 23 days. Between 5 and 10 days after Amphenone therapy was begun there was a marked increase in sodium excretion from 7 mEq. to a maximum of 155 mEq. per day. There was an accompanying water diuresis and weight loss of 7 kg. (Fig. 1).

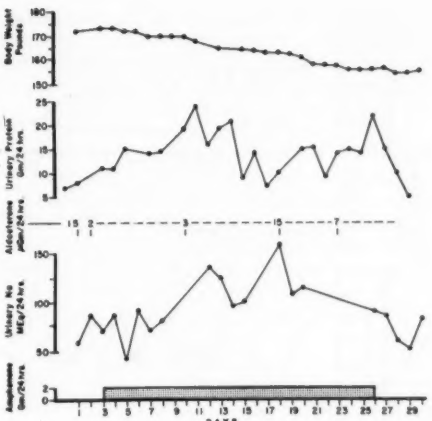

Fig. 1.—The effect of Amphenone on urinary sodium, aldosterone, and protein levels and on body weight in Patient 1, with nephrotic edema resulting from Kimmelstiel-Wilson syndrome.

The urinary protein levels as well as the variable and inconsistent urinary levels of aldosterone are illustrated in Figure 1. Much of the aldosterone was thought to have been trapped in the protein-lipid emulsion which formed during hydrolysis and extraction, and therefore an interpretation of these levels would be meaningless.

There were no adverse effects from the Amphenone. After the first few days of therapy, his edema, vision, appetite, and sensorium improved markedly and he was able to be ambulatory. Thereafter there was progressive improvement, with complete loss of edema.

As illustrated in Figure 2, a tendency toward glucocorticoid suppression during Amphenone treatment is suggested by the decrease in urinary 17-hydroxycorticosteroid levels from a pretreatment mean of 5.8 mg. per 24 hours to less than 3.7 and 3.5 mg. per 24 hours ($P<0.05$) during treatment. Further evidence of glucocorticoid suppression is the decrease in mean daily insulin requirement from 39 units for the first half to 29 units for the second half of treatment. Fasting blood sugar levels also decreased despite a smaller

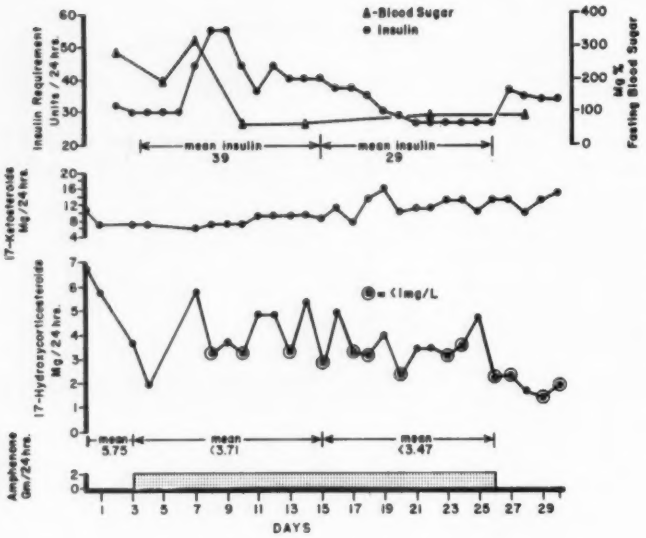

Fig. 2.—The effect of Amphenone on urinary 17-hydroxycorticosteroid and 17-ketosteroid levels and on insulin requirement in Patient 1, with nephrotic edema resulting from Kimmelstiel-Wilson syndrome. When the urine specimens contained less than 1 mg. of 17-hydroxycorticosteroid material per liter, the content is recorded as less than (<) the amount calculated on the basis of 1 mg. per liter.

daily insulin dose and markedly increased food intake. Other workers, in acute experiments of one to four days of oral Amphenone administration, did not find suppression of glucocorticoid secretion in patients with normal pituitary and adrenal function, although definite suppression was obtained in patients receiving adrenocorticotropin and in patients with adrenal cortical carcinoma.[18] Evidence of glucocorticoid suppression was only seen after five days of Amphenone treatment in the presently reported case and became progressively more apparent as treatment was continued. Urinary 17-ketosteroid levels did not change significantly, although there was a slight increase during Amphenone treatment, which has been noted by other workers.[19]

At the end of the third week of therapy, the patient's blood pressure had decreased from 210/110 to 180/80 and he had weakness and faintness on standing. After discontinuing Amphenone and increasing his sodium intake to 50 mEq. per day, these symptoms disappeared and his blood pressure stabilized at 200/100.

Renal biopsies performed before and after Amphenone therapy revealed only Kimmelstiel-Wilson lesions and no changes which could be attributed to Amphenone. A 24-hour radioactive iodine uptake over the thyroid was reduced from a pretreatment level of 25% to 6% during therapy, as would be expected.[10]

After having been essentially asymptomatic for six months on the usual regimen for diabetes, he had another severe exacerbation of the nephrotic syndrome. Amphenone was again given for four days before death but without response. The renal lesions at autopsy were unchanged over those obtained previously.

Congestive Heart Failure: Patient 2, a 34-year-old man had acute rheumatic fever at 7 years of age but had been asymptomatic until 30 years of age when he was found to have congestive heart failure with aortic and mitral stenosis. At 32 years of age he had an aortic and mitral valvulotomy. He was fairly well maintained on the usual treatment until two months prior to

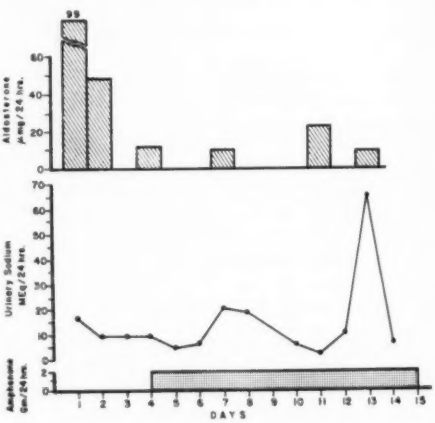

Fig. 3.—The effect of Amphenone on urinary sodium and aldosterone levels in Patient 2, with congestive heart failure resulting from rheumatic aortic and mitral stenosis. There was no consistent effect on urinary sodium levels, although the markedly elevated aldosterone levels were reduced to normal by Amphenone.

entry, at which time he developed intractable congestive heart failure with severe edema, ascites, and hydrothorax. He became progressively worse despite an intensive diuretic program. Urinary aldosterone levels were between 50μg. and 99μg. per 24 hours (Fig. 3). Amphenone was given for 11 days without toxic effects. Urinary aldosterone levels were decreased to 10μg. on the first day of treatment and remained around this level throughout the course of treatment (Fig. 3). Despite this, there were no consistent changes in urinary sodium levels, urinary output, edema, or clinical picture. There were no changes in either the urinary 17-hydroxycorticosteroid or 17-ketosteroid levels. This patient later died, and his severe rheumatic aortic and mitral stenosis was confirmed at autopsy.

Another patient with intractable congestive heart failure and edema resulting from arteriosclerotic heart disease was also given Amphenone in a similar manner, with no toxic effects and no effect on sodium or water excretion.

The fact that sodium and water diuresis failed to occur, even though aldosterone levels were reduced to normal by Amphenone, implies that mechanisms other than aldosterone were more important in these patients' edema formation. This same phenomenon has been previously noted.[20]

Cirrhosis of the Liver: Amphenone was also administered intravenously and orally, as described, to two patients with far-advanced cirrhosis of the liver. Both patients had had ascites which required weekly paracenteses for several months prior to entry. Within one hour after beginning the intravenous infusion, both patients developed confusion and semistupor resembling hepatic coma, which would clear within two hours after discontinuing the treatment. Therapy was terminated after two days in both patients because of these side-effects. No effect was noted on either sodium or water excretion during this short period of Amphenone administration, although urinary aldosterone levels were decreased from a pretreatment mean of 30μg. to a mean of 9μg. per 24 hours during treatment.

The presence of two amino groups in the Amphenone molecule, together with the unique reaction of these patients with cirrhosis to this small amount of Amphenone, suggested the possibility of elevated ammonia levels as a cause of this reaction. Consequently, a 1% solution of freshly dissolved Amphenone was assayed and found to contain 0μg. % to 20μg. % of ammonia; when allowed to stand for three days it contained 50μg. %, and after three weeks it contained 250μg. % of ammonia. The blood ammonia level of a patient given intravenous Amphenone as described did not change significantly. It would appear therefore that factors other than ammonia, such as the inherent sedative effect of Amphenone, are responsible for the reaction in these patients.

Others workers have been able to prevent these toxic manifestations and to effect a decrease in urinary aldosterone and a sodium and water diuresis in similar patients by the simultaneous administration of Amphenone and prednisone.[21]

Primary Hyperaldosteronism.—Patient 3, a 54-year-old white man was admitted to the hospital because of hypertension. He had been in good health until 12 years prior to admission when he developed very mild generalized headaches which were worse in the afternoons and usually relieved by aspirin. His blood pressure had been consistently elevated for 12 years, although some degree of control (diastolic 110±10 mm. Hg) had been obtained in the past six years with weight reduction, salt restriction, hydrolazine (Apresoline), rauwolfia, and hexamethonium. There was no history of orthopnea, dyspnea, edema, chest pain, or attacks of weakness, paralysis, flushing, paleness, sweating, or nervousness. He had had nocturia for four years but no polyuria or polydipsia.

In 1955, he had had a cholecystectomy and a common-duct stone removed after right upper quadrant pain and jaundice. His father had died of asthma and heart disease, his mother died at childbirth, and one sister has hypertension.

He was slightly obese, well-developed, and in no distress. His pulse was 82 per minute, respirations 20 per minute, weight 195 lb., and blood pressure 210/140 mm. Hg in both arms sitting. The pulses were normal in the upper and lower extremities. His fundi revealed moderate AV nicking and arterial narrowing but no exudates or hemorrhages. The thyroid was slightly enlarged. The PMI was not felt, but the apical heart sounds were heard best in the fifth intercostal space in the midclavicular line. The rhythm was regular and A_2 was greater than P_2. There was a Grade I aortic systolic murmur which did not radiate. The abdomen was protuberant, but there were no masses or tenderness. The prostate was moderately enlarged without tenderness or nodularity. The neurological examination was normal.

Two months prior to admission he was found to have an elevated urinary aldosterone level of 28μg. per 24 hours, a serum potassium level of 2.5 mEq. per liter, a mild alkalosis with a plasma carbon dioxide level of 32 mEq. per liter, and an alkaline urine.

On entry to the hospital the packed cell volume was 45%, the white blood cell count was 6,000 with a normal differential, and the urine was constantly alkaline (pH 7.5), with a specific gravity of 1.011 and with no protein or formed elements in the sediment. The blood urea nitrogen level was 20mg. %, serum sodium level 152 mEq. per liter, serum potassium level 3.0 mEq. per liter, and serum CO_2 level 33 mEq. per liter. In addition, the following serum levels were ob-

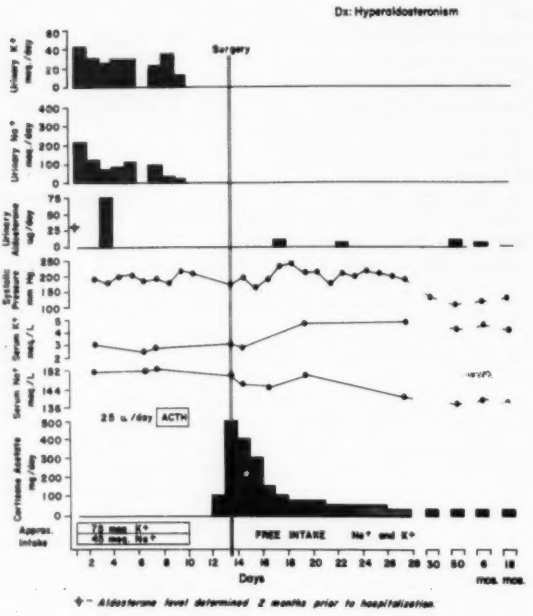

Fig. 4.—The clinical course of Patient 3, with primary hyperaldosteronism resulting from bilateral adrenal hyperplasia. Surgery consisted of subtotal bilateral adrenalectomy, after which there was a return to normal of the blood pressure and serum sodium and potassium and urinary aldosterone levels which have remained normal for the 18-month follow-up period. Note the relatively high urinary potassium levels when the serum potassium levels were very low.

tained: calcium, 10µg. %; phosphorus, 3.7 mg. %, and uric acid, 8.5 mg. %. The chest film was clear except for a small calcified nodule in the right lateral chest. The upright film of the abdomen showed kidneys of normal size and position; but a 3-4 mm. calcification was present in the upper pole of the right kidney and in the middle pole of the left kidney within the pelvic area.

The fasting blood sugar level was 85 mg. %, and the one- and two-hour postprandial levels were 173 and 123 mg. %, respectively. On a diet containing approximately 45 mEq. of sodium and 75 mEq. of potassium, the serum sodium level ranged from 150 to 152 mEq. per liter and the serum potassium level from 2.7 to 2.9 mEq. per liter (Fig. 4). Despite the high serum sodium levels, the urinary sodium levels decreased to 45 mEq. per day, and, although the potassium balance remained positive, urinary potassium levels averaged 30 mEq. per day in spite of the low serum potassium levels. The urinary aldosterone level was 77µg. per 24 hours on the third day of study (Fig. 4).

The urinary 17-hydroxycorticosteroid and 17-ketosteroid response to corticotropin administered intravenously over eight hours on two successive days was high normal. The mean control 17-hydroxycorticosteroid level was 6.75 mg. per 24 hours, and the increase above the control level was 22.04 mg. on the first day and 33.78 mg. on the second day of corticotropin administration. The mean control 17-ketosteroid level was 8.60 mg. per 24 hours, and the increase above the control was 6.41 mg. on the first day and 7.49 mg. on the second day of corticotropin administration.

Prior to surgery, the patient's blood pressure ranged from 236 to 160 mm. Hg systolic and from 160 to 100 mm. Hg diastolic (Fig. 4). Bilateral adrenal exploration and removal of the entire right adrenal and approximately 90% of the left adrenal was performed on the 13th day. Although both adrenals appeared normal at operation, histological examination revealed nodular hyperplasia and arteriosclerosis. During the operation the patient was given replacement cortisone, and the dose was gradually tapered postoperatively to a maintainence level of 37.5 mg. per day, given orally in three divided doses. He tolerated the procedure well, and four days after operation his serum sodium and potassium levels returned to normal (Fig. 4). At the same time his serum CO_2 level decreased to 20 mEq. per liter and his urine pH to 4.5. Approximately three weeks after operation his blood pressure began to decrease and five weeks postoperatively reached levels of 110/80 mm. Hg, where it has remained for the 18-month follow-up period (Fig. 4). Corticotropin administration on numerous occasions since operation have resulted in an inadequate adrenal cortical response and cortisone withdrawal on one occasion resulted in signs and symptoms of glucocorticoid deficiency. His carbohydrate tolerance has returned

to normal as evidenced by a two-hour postprandial blood sugar level of 70 mg. %. Repeated urinary aldosterone levels since operation have remained between 5μg. and 8μg. per 24 hours. We have no explanation at present for the presence of this material, which is assayed as aldosterone, although more definitive identification procedures are under way.

After being maintained on cortisone alone for 18 months, he has remained active and asymptomatic. His blood urea nitrogen level has remained around 26 mg. %, his serum sodium level from 135 to 140 mEq. per liter, and his serum potassium has risen to levels ranging from 5.1 to 5.8 mEq. per liter.

There are now numerous cases reported of primary hyperaldosteronism resulting from an adenoma of the adrenal,[22] and at least one case in which the syndrome resulted from an adrenal carcinoma.[23] Although there are only five cases reported of primary hyperaldosteronism caused by bilateral hyperplasia of the adrenal cortex,[24-28] many more cases undoubtedly exist which have not been reported. The importance of these cases is that at operation the surgeon may be faced with the problem of removing what appear to be normal adrenals, as happened with the presently reported case. To confuse the issue further, urinary aldosterone levels may be normal [26] and the patient may be completely asymptomatic except for hypertension. The present use of antihypertensive drugs which cause potassium diuresis and consequent hypokalemia further compounds the diagnostic difficulty. Ancillary findings, such as carbohydrate abnormalities, as have been reported [28] and as were present in this patient, may be helpful in the final decision for adrenalectomy.

Primary Hypoaldosteronism.—Patient 4, a 62-year-old white male carpenter, entered the hospital because of shortness of breath, "blackout" spells, and muscle, bone, and stomach pain. He dated all of his illness to the First World War and had had numerous hospital admissions because of these complaints.

The shortness of breath developed after an episode of gassing during the First World War. It had slowly progressed to the point where he was dyspneic at rest. The diagnosis of pulmonary fibrosis, obstructive pulmonary emphysema, and cor pulmonale had been made in the past. Digitalis leaf and isoproterenol hydrochloride aerosol, started a year before his final admission, had given the patient moderate relief. He had stopped all medications some time before entry and was again in respiratory distress.

The musculoskeletal pains were generalized with no associated joint redness, swelling, or deformity. The pain was characterized by stiffness in the morning with some relief after activity and rather constant generalized muscle tenderness.

In 1954, a subtotal gastrectomy was performed after a long history of epigastric pain and frequent melena. Prior to surgery a large penetrating ulcer was demonstrated on the lesser curvature just above the angularis. Since operation the patient had had frequent episodes of cramping abdominal pain and almost daily bouts of postprandial dizziness, weakness, numbness, and shortness of breath which sometimes resulted in syncope. Other episodes of temporary loss of consciousness were not associated with hyperventilation and were not related to position, time of day, activity, or eating. They occurred once or twice a week and lasted two to three minutes and were accompanied by a feeling of cessation of heart beat. He was never observed by a physician during one of these episodes.

He was well developed and mildly dyspneic at rest. The skin and mucous membranes were not abnormally pigmented and the hair distribution was that of a normal adult man. His blood pressure was 190/90, pulse 84 per minute, and respirations 22 per minute. Fundiscopic examination revealed slight AV nicking but no hemorrhages, exudates, or papilledema. The thyroid was not palpable, and no venous distention or tracheal deviation was noted. There was an increase in the AP diameter of the chest and a moderate cervical kyphosis. Moist exspiratory and inspiratory rales were heard at both lung bases. The cardiac PMI was diffuse in the fifth intercostal space just outside the midclavicular line. A normal sinus rhythm interrupted by an occasional premature contraction was present, and no murmurs were heard. The abdomen was soft and moderately tender in all areas. No abdominal organs or masses were palpated. The prostate was slightly enlarged, soft, and nontender. Two-plus pitting pedal and pretibial edema was present. The reflexes were equal bilaterally but were hyperactive in the upper extremities and

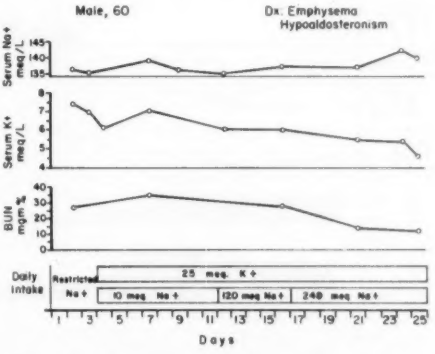

Fig. 5.—The response of the serum sodium and potassium and blood urea nitrogen levels to variations in sodium intake during constant potassium intake in Patient 4, with hypoaldosteronism.

decreased in the lower. The corneal reflex was decreased on the left, and a left abducens paresis was present.

The hemoglobin concentration was 11.25 gm. % with a normal white blood cell count and differential. The urine was acid, negative for sugar, and contained 1+ protein. The sediment contained 2 to 5 white blood cells, an occasional red blood cell, and 0 to 1 coarsely granular cast per high-powered field. A sputum culture contained a mixture flora with β-hemolytic streptococci as the predominant pathogen. The serology was negative. An electrocardiogram revealed a normal sinus rhythm with a rate of 80 per minute, interrupted by multifocal premature ventricular and auricular contractions. Nonspecific *T*-wave changes were present. The chest film demonstrated emphysema and interstitial fibrosis associated with spotty calcification in both hilar regions. The only change from his previous chest films was a slight elevation of the left diaphragm. The only abnormality seen on a plain film of the abdomen was venous calcification in the pelvis. X-rays of the stomach and colon revealed a diverticulum of the gastric pouch which was thought to be traction in type and a normal large bowel. No marginal ulcers could be demonstrated at the site of the previous operation. On skull films a calcified area overlying the sella turcica was seen. This was interpreted as a calcified placque in the carotid siphon.

The patient was placed on digitalis, a low sodium diet, and mercurial diuretics. Over the next several days he lost 10 lb. of weight but complained of increasing weakness, anorexia, and vomiting of small amounts of greenish material. After complete digitalization his edema has disappeared, his dyspnea had improved markedly but not completely, and the rales had disappeared from the chest. At this time the serum potassium level was 7.4 mEq., sodium 136 mEq., CO_2 23 mEq., and chloride 108 mEq. per liter, and the blood urea nitrogen was 27 mg. %.

A phenolsulfonphthalein test done at this time revealed that 15% of the dye was excreted in

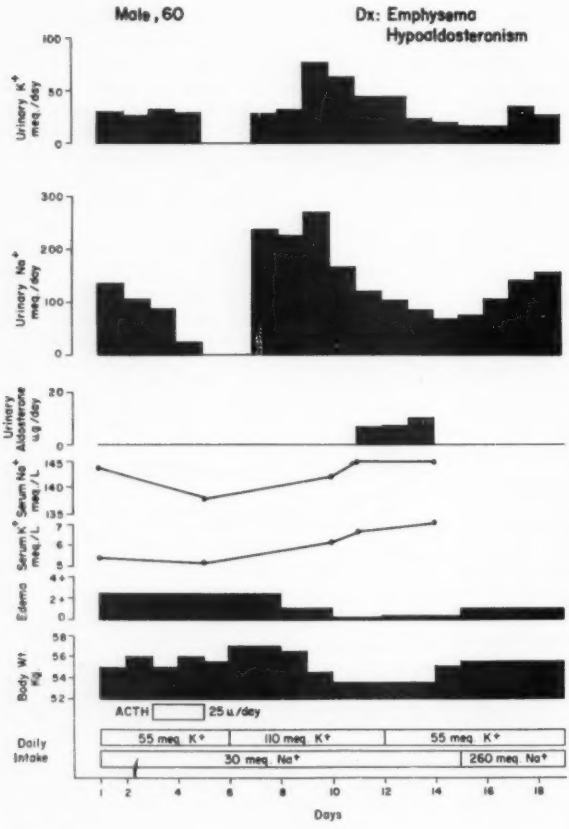

Fig. 6.—The response of urinary sodium, potassium and aldosterone, and serum sodium and potassium levels, edema, and body weight to variations in potassium intake during sodium restriction in Patient 4, with hypoaldosteronism. Serum sodium levels rose during increased potassium intake with a marked sodium and water diuresis and loss of 4 kg. in body weight. At the same time serum potassium levels rose markedly because of the inability of the kidney to excrete the added potassium load.

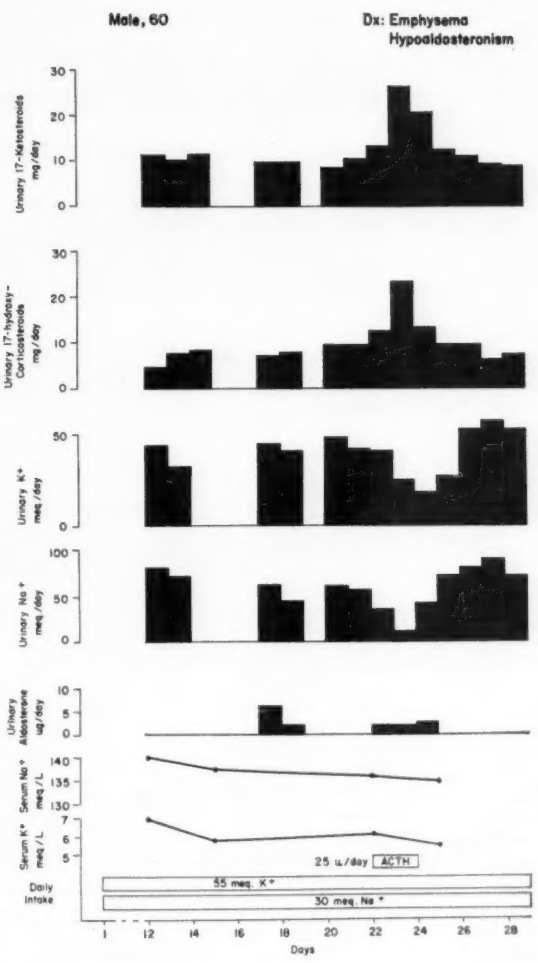

Fig. 7.—The response of urinary 17-hydroxycorticosteroid, 17-ketosteroid, aldosterone, sodium and potassium, and serum sodium and potassium levels to sodium restriction and corticotropin administration in Patient 4, with hypoaldosteronism.

15 minutes and 40% in two hours. This was repeated several months later, at which time 35% of the dye was excreted in 15 minutes and 85% in two hours. The urea clearance was 48% and 50% on two occasions. The inulin clearance was 151 ml. per minute and the para-aminohippurate clearance was 380 ml. per minute. Specimens of urine collected at random showed specific gravities up to 1.024. His 24 hour urinary output averaged 1,500 ml. The blood urea nitrogen level varied from 37 to 12 mg. %, the serum potassium level from 7.4 to 5.4 mEq. per liter, and the serum sodium level from 135 to 142 mEq. per liter (Figs. 5-8).

Although these data suggested that this patient did not have severe enough renal damage to cause this degree of hyperkalemia, the blood urea nitrogen and serum potassium levels tended to parallel each other and both decreased with increasing sodium intake (Fig. 5). This phenomenon is characteristic of Addison's disease but has also been shown to occur in patients with combined renal damage and mineralocorticoid deficiency and in the presence of adequate glucocorticoid replacement therapy.[7,30,33] The fact that this patient did not have Addison's disease is proved by the normal response of the urinary 17-hydroxycorticosteroids and 17-ketosteroids to the intravenous administration of corticotropin, as illustrated in Figure 7. In addition, the fact that his renal tubules were capable of responding by sodium retention and slight potassium diuresis to administration of a potent mineralocorticoid, such as desoxycorticosterone acetate, is illustrated in Figure 9.

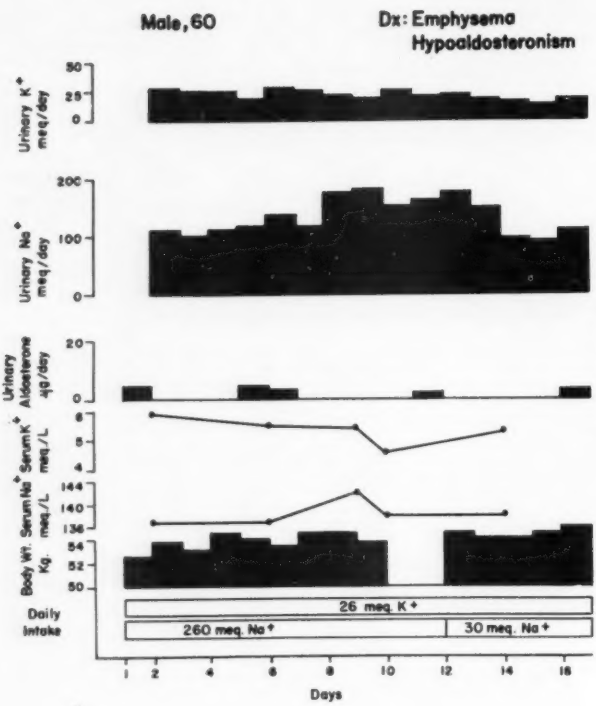

Fig. 8.—The response of urinary aldosterone, sodium and potassium and serum sodium and potassium levels, and body weight to variation in sodium intake in Patient 4, with hypoaldosteronism.

In contrast to studies on normal subjects, as illustrated in Figures 10 and 11 and as reported by other workers,[23-25] urinary aldosterone levels could not be increased significantly by sodium deprivation or potassium loading (Figs. 6-8). The majority of the aldosterone levels ranged from 1μg. to 4μg. per 24 hours, and the highest levels obtained were 7μg. and 10μg. per 24 hours while on a daily intake of 30 mEq. of sodium and 110 mEq. of potassium (Fig. 6). These levels of aldosterone were much lower than those obtained in normal subjects on a similar sodium intake and less provocative potassium intake of 55 to 77 mEq. per day (Figs. 10 and 11). The kidney function tests and the normal 17-hydroxycorticosteroid and 17-ketosteroid excretion in this patient are evidence against renal damage being a cause of the decreased urinary aldosterone levels. There was a general tendency for a negative sodium and positive potassium balance despite the relative decrease in serum sodium and increase in serum potassium levels (Figs. 6-9). In addition, potassium loading resulted in a sodium and water diuresis and an increase in serum potassium and sodium levels (Fig. 6).

As would be anticipated in any patient with adrenal cortical insufficiency, especially of miner-

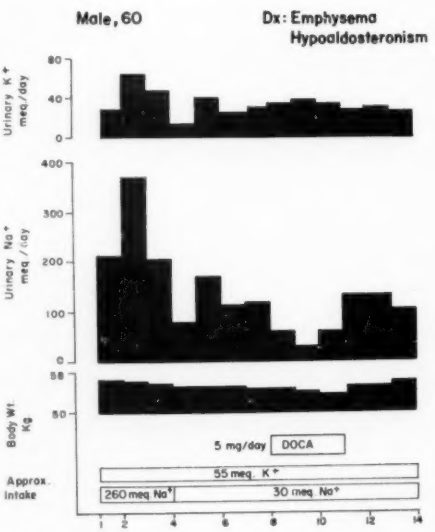

Fig. 9.—The response of urinary potassium and sodium levels and body weight to 5 mg. of deoxycorticosterone acetate administered intramuscularly daily for three days to Patient 4, with hypoaldosteronism.

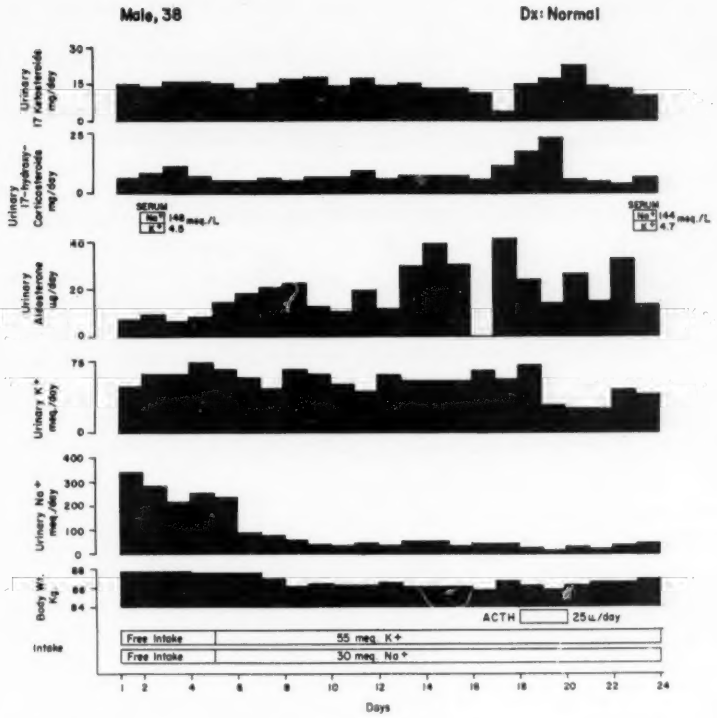

Fig. 10.—The response of urinary 17-ketosteroid, 17-hydroxycorticosteroid, aldosterone, potassium, and sodium levels and of body weight to sodium restriction and corticotropin administration in a normal subject.

alocorticoids, the presently reported patient could not tolerate either severe sodium restriction or potassium loading, unless deoxycorticosterone was simultaneously administered. He was, however, fairly well maintained on a moderately high sodium and moderately low potassium intake of 150 and 55 mEq. per day, respectively, without added steroids. The clinical findings in the two cases reported as representing primary hypoaldosteronism are very different,[5,6] and the findings in the present case are strikingly similar to those in the patient reported by Hudson, Chobanian, and Relman.[5] In contrast to the patient reported by Skanse and Hökfelt,[6] the urinary 17-hydroxycorticosteroid excretion of the present patient did not increase on prolonged sodium restriction (Fig. 7). The question as to how much of the clinical picture in the present case can be attributed to the inadequate aldosterone response and how much to renal disease cannot be completely answered, although the studies favor the former as the dominant cause of the findings.

Studies in Normal Subjects.—One normal subject (Fig. 10), who was studied for 24 days, demonstrates the step-wise increase in aldosterone and decline in urinary sodium levels over a five-day period following sodium restriction. After coming into sodium balance, urinary aldosterone

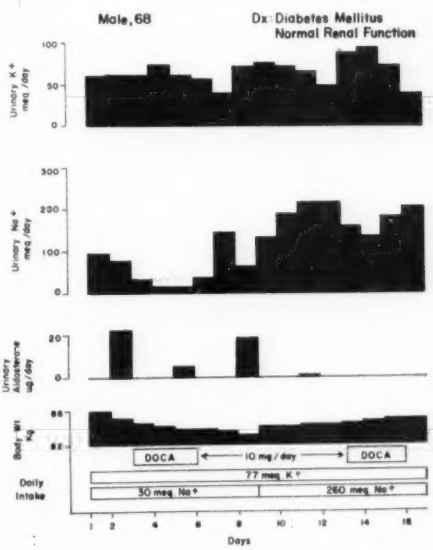

Fig. 11.—The response of urinary potassium, sodium, and aldosterone levels and of body weight to variations in sodium intake and to deoxycorticosterone acetate administration to Patient 5, without known adrenal or renal abnormalities.

levels, which had more than doubled during this initial period, became somewhat erratic, although, during the 19 days of sodium restriction, they never became as low as the baseline levels. During this period there were no significant changes in the urinary 17-hydroxycorticosteroid or 17-ketosteroid levels nor in serum sodium or potassium concentration. Corticotropin administration during the period of sodium restriction did not alter urinary aldosterone levels.

Another patient, Patient 5, without known adrenal or renal abnormality (Fig. 11), who was studied for 17 days, again demonstrates the increased urinary aldosterone levels accompanying sodium restriction. These increased levels were markedly inhibited by the administration of deoxycorticosterone acetate or by increasing the sodium intake. The sodium-retaining and slight potassium diuretic effect of deoxycorticosterone acetate during periods of both high and low sodium intake are also demonstrated by this patient.

Comment

It is apparent from the studies on patients with secondary hyperaldosteronism that Amphenone may be administered intravenously in small amounts for at least 23 days without toxic effects, except when severe liver disease is present. The patients with cirrhosis of the liver did not tolerate the intravenous administration of even very small amounts of Amphenone because of the development of semistupor. The stupor resembled hepatic coma but was not associated with elevated blood ammonia levels. In the patient with nephrosis, Amphenone, administered in this manner, induced a twofold increase in sodium excretion, a marked water diuresis, and a clinical remission beginning 10 days after initiating therapy. Glucocorticoid suppression also began about five days after starting Amphenone. In two patients with severe congestive heart failure sodium and water diuresis failed to occur even though elevated urinary aldosterone levels were reduced to normal by Amphenone administration. This implies that other abnormalities, presumably hemodynamic, are more important than elevated aldosterone levels in causing and maintaining edema in these patients with congestive heart failure.

Patients with primary hyperaldosteronism may be completely asymptomatic except for hypertension, as demonstrated by the patient reported. In this patient, severe hypertension of 12 years' duration was completely ameliorated by the subtotal removal of bilaterally hyperplastic adrenals, which emphasizes the necessity of correct diagnosis and definitive surgery. A decreased serum potassium level assumes major diagnostic importance in these patients, as symptoms suggesting hypokalemia may be absent and urinary aldosterone levels may either not be consistently elevated or be elevated secondarily. The use of antihypertensive drugs which cause potassium diuresis and consequent hypokalemia makes this diagnostic index also open to question. However, in the majority of patients treated with these compounds the serum sodium concentration is low rather than normal or high as seen in patients with hyperaldosteronism. If, at the time of adrenal exploration, an adrenal adenoma is found, the surgeon's course of action is clear. If, however, the adrenals appear normal, the diagnosis should have been well enough established beforehand to be able to advise subtotal adrenalectomy despite this. The most satisfactory method now readily available for making such a diagnosis continues to be the repeated determination of serum sodium and potassium levels, taking into consideration the difficulties already mentioned.

An absolute or relative deficiency of aldosterone might logically be expected to produce abnormalities in the body's ability to handle sodium and potassium. Of the two cases reported as representing such a deficiency,[5,6] only one demonstrated these electrolyte abnormalities.[5] The present case represents another instance in which a relative primary deficiency of aldosterone has been demonstrated along with abnormalities primarily in potassium metabolism. A similar clinical picture has also been seen in patients with combined renal damage and mineralocorticoid deficiency.[7,30,31] Patients with total bilateral adrenalectomy being

maintained on glucocorticoids alone do not always manifest abnormalities in potassium metabolism.[7,30] It is possible, however, that the follow-up has not been long enough or that the dietary conditions have not been provocative enough for these patients to demonstrate this syndrome. The production of a hypothetical antialdosterone substance could theoretically produce electrolyte abnormalities identical to those reported. Under these circumstances, however, one would anticipate a decreased response to deoxycorticosterone acetate (DOCA) which was not seen in the presently reported case nor in the case reported by Hudson, Chobanian, and Relman,[5] although the amounts of deoxycorticosterone acetate given both patients were greater than physiologic replacement. Furthermore, one would not expect decreased aldosterone excretion under these circumstances. The role of digitalis and congestive heart failure in the electrolyte changes noted in both of these patients can only be speculative. These are speculations, and, as renal damage plus mineralocorticoid deficiency has produced findings similar to those in the present patient, we shall attribute this syndrome to the latter combination of circumstances until additional information is available.

Summary

Urinary aldosterone, 17-hydroxycorticosteroid, 17-ketosteroid, and electrolyte changes have been studied during control periods, periods of inhibition of adrenal cortical secretory activity by Amphenone (3,3-bis[*p*-aminophenyl]-2-butanone), and periods of stimulation by sodium withdrawal and potassium administration in patients with (*a*) secondary hyperaldosteronism, (*b*) primary hyperaldosteronism, and (*c*) primary hypoaldosteronism. These studies have been compared with similar ones made on normal subjects. Amphenone inhibits aldosterone excretion and may or may not lead to sodium diuresis. Bilateral adrenalectomy ameliorates hypertension of 12 years' duration in the sixth reported patient with primary hyperaldosteronism resulting from bilateral adrenal hyperplasia. The syndrome of primary hypoaldosteronism is reevaluated in light of studies on subjects with bilateral adrenalectomy maintained on cortisone.

Assistance was given by Miss Mary Sheffield, Mrs. Hilda Harris, Miss Minnie Mae Tims, Dr. Jacques Genest, Dr. H. V. Murdaugh, Dr. H. Brad Morris, and Dr. Thomas Patton.

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Reviews of Internal Medicine

The Problem of Gastric Ulcer

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Introduction

There are two principal attitudes in the management of gastric ulcer. The prevailing surgical opinion is that all gastric ulcers should be removed promptly.[1-3] The opposing view, held by numerous physicians and some surgeons, is that gastric ulcer can be dealt with individually: Many patients respond to medical management and others require resection.[4-6] The purpose of this paper is to examine the problem, on the basis of evidence in the literature and our clinical experience, in relation to four major issues. These are (*a*) differentiation of benign and malignant gastric ulcer, (*b*) the alleged hazard of neoplasia, (*c*) improvement of the survival rate of gastric cancer by the routine resection of gastric ulcer, and (*d*) the advantages and limitations of medical and surgical treatment.

General Observations

Gastric ulcer resembles duodenal ulcer in clinical manifestations, course, and in response to treatment.[7-9] The pain mechanism, acid irritation of nerve endings exposed in the ulcer crater, is the same. Hemorrhage and perforation occur in both, but in contrast to duodenal ulcer, jejunal ulcer is uncommon after gastroenterostomy for gastric ulcer. Gastric ulcer also differs from duodenal ulcer in that the secretion of hydrochloric acid usually is intermittent and normal or subnormal. Tissue vulnerability rather than excessive acid appears to be a major pathogenetic factor. Nevertheless, the digestive power of the gastric content, albeit less than in duodenal ulcer, exceeds the lowered resistance of the susceptible gastric mucosa, and sustained neutralization or elimination of hydrochloric acid results in complete healing of the ulcer (Case 1). According to Dragstedt,[10] the stimulus for secretion in gastric ulcer is chiefly hormonal (antral) in origin, whereas the hypersecretion in duodenal ulcer is mediated principally over the vagus nerves. The tissue vulnerability in gastric ulcer remains unexplained; factors such as the mucous barrier of the stomach, vascular abnormalities, diminished regenerative capacity of the atrophic gastric mucosa, and defects in intracellular enzyme systems of gastric epithelium may be involved. The possible role of endocrine influences (originating in the adrenals, pancreas, parathyroids, and pituitary) upon tissue resistance and gastric secretion in peptic ulcer also has been emphasized.[12]

Gastric Ulcer—Diagnostic Index
(293 Patients—1950-1958)

Procedure	Surgery (105 Patients)	Medicine (58 Patients)	Gastroenterology (130 Patients)
Gastric analysis	69-.66	42- .72	121-.93
Stools/Blood	41-.39	49- .84	114-.88
Gastroscopy	42-.40	31- .53	112-.86
X-Ray	93-.89	58-1.0	129-.99
Cytology	49-.46	47- .81	99-.76
Index (per patient)	2.8	3.9	4.4

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According to Lilja,[13] gastric ulcers located at the angulus may diminish peristaltic and motor activity.

The proportion of gastric to duodenal ulcer is in a ratio of 1:4. Gastric ulcer is more frequent among women than is duodenal ulcer. Differing occupational, epidemiological, and psychiatric relationships also have been suggested.[14] Gastric ulcer follows the usual age distribution of peptic ulcer but may develop after the age of 65.[15] The incidence appears to be increased in patients with emphysema and other chronic pulmonary diseases [16] as well as among persons with congestive heart failure.[17] Benign gastric ulcer may be acute [18] or chronic, single or multiple,[19] and duodenal ulcers coexist in 15% to 20% of cases. Benign gastric ulcers may be very large,[20-22] exceeding 3 or 4 cm. in diameter, or very small,[23] approximating 2 or 3 mm; the usual range is 1 to 2 cm. diameter and 0.5 to 1 cm. in depth.[24] Benign ulcers occur anywhere in the stomach, including the prepyloric area and the greater curvature,[25-27] but they are most frequent on the lesser curvature of the body of the stomach, proximal to the angulus.[24,28] Gastric ulcers may develop rapidly and heal promptly, or they may be chronic, persisting for months and years. The increasing size of an ulcer crater, in accord with its penetrating nature, denotes extension from the mucosa through the gastric wall and is not indicative of malignancy.[29] Complications, including hemorrhage, obstruction, and perforation, develop in approximately 50% of cases. The natural tendency of benign gastric ulcer is toward healing; the circumstances promoting chronicity are not understood completely, but they include poor general health of the patient, delayed gastric emptying, penetration of the ulcer into the pancreas (among other complications), and inadequate control of the acid gastric secretion.

Differential Diagnosis

Diagnostic Error and Accuracy.—Statistically, most gastric ulcers are benign. Bachrach [30] has estimated an error of approximately 15% or 20% if all ulcerating gastric lesions, without study, were deliberately pronounced benign. If the obviously malignant lesions were discarded and the remainder pronounced benign, the error would not be in excess of 7%. Careful study, in our opinion, should be productive of a reduction of 3 or 4% or less. The pessimistic attitude toward the differential diagnosis of gastric ulcer seems attributable to at least two observations; the histologic demonstration of carcinoma in approximately 10% to 20% of gastric ulcers clinically considered benign and the inability of the surgeon to identify the lesion correctly at operation.[31-45] In representative series, the diagnostic error was 7% of 512 patients,[34] 12% of 186 cases,[39] 13% of 550 patients,[37] and 29% of 198 cases.[46] Errors occur much oftener in evaluating a benign lesion as malignant and proceeding with surgery than in the reverse. Thus, the 34 carcinomas among 512 patients included 32 of the 295 patients undergoing resection.[34] In another series, carcinoma was diagnosed in 56 of 196 cases operated on (28.6%),[46] but 231 additional patients with gastric ulcer were treated medically in the same institution; the error for the total series of 427 persons, accordingly, might be readjusted to 13%. In another report, carcinoma was encountered in 34 of 92 surgically treated patients (37%) and in 13 of 175 patients treated medically (7%).[32] Perhaps the term "true error" might be reserved for those ulcerating gastric carcinomas erroneously receiving prolonged medical management, and the term "conditional error" might be applied to those malignant ulcers tentatively grouped as benign but with so little conviction as to promptly undergo resection.

Many diagnostic reports are difficult to evaluate because of insufficient information as to methods of study and the basis for diagnosis. Considerable dependence appears to have been placed upon the retrospective analysis of patients' records. Unless charts

have been maintained scrupulously and the final preoperative diagnosis carefully recorded, such data may be extremely inaccurate (as demonstrated in a recent survey at the University of Chicago). Too often, the only recorded preoperative diagnosis on the operation sheet was simply "gastric ulcer," unqualified as to benignancy or malignancy—though this differentiation had been made.

The accuracy of the gross examination of the stomach at operation has been overemphasized.[41,42,46,47] The surgeon palpating a gastric ulcer through the serosal surface may be in a less advantageous position diagnostically than the radiologist or the clinician, except in dealing with the more obvious lesions.[48,49] The presence of enlarged regional lymph nodes, in the absence of histological examination, is not necessarily diagnostic of neoplasm. The limitations of inspection and palpation at operation have led to the use of local gastric biopsy with quick-frozen sections as a more accurate approach.[50,51] Experienced pathologists have recognized that the edematous, congested, freshly obtained specimen may be less diagnostic grossly than the "fixed" tissue.[52]

An important defect of many surveys is the apparently inadequate method of study. Diagnosis often appears to have been based upon a single roentgen examination (or two such procedures within several weeks), omitting gastric analysis, examination of the feces for occult blood, gastroscopy, and—in recent years—exfoliative cytology. Information also is lacking concerning the number of studies, as well as the experience and skill of the examiners. The enormous variation in the diagnostic approach to gastric ulcer is illustrated by a recent survey of 293 patients at the University of Chicago, observed during the period from 1950 to 1958.[53] Of these, 105 were managed by surgeons; 58, by various medical services, and 130, by the gastroenterology service. Based upon the single use of five procedures (Table), the diagnostic index was, for surgeons, 2.8; for internists, 3.9, and for gastroenterologists, 4.4. The record for gastroenterologists also was much superior in the number of repeat examinations. These and similar data indicate a possible explanation for the variable results on differential diagnosis.

Many diagnostic surveys are favorable. Representative errors include 4.5% of 50 patients (chiefly based upon x-rays),[54] 3% of 138 patients,[55] 2.0% of 1,000 patients,[56] 2.9% of 908 cases,[57] and 1.5% of 130 patients.[58] In a series of 342 patients, 36 ulcers suspected as malignant were benign, and only 13 ulcers evaluated as benign proved to be malignant. Among 161 persons with "benign-appearing" gastric ulcer, carcinoma was diagnosed later in 8 of 88 cases operated upon and in one of 73 patients treated medically,[60] again illustrating the low "true" error. Among 200 patients evaluated in 1954—the studies included gastroscopy and exfoliative cytology—the diagnostic error was only one per cent, and the two patients with carcinoma were operated upon.[61] A subsequent survey from the same group concerned 228 cases; 177 diagnosed as benign were treated medically, and the 51 cases which underwent resection included two with malignancies, a total error of 0.9%.[62] A series of 100 gastric ulcers included two lymphomas and one carcinoma; gastroscopy was especially helpful, though the total study was emphasized.[63] We reported a series of 121 patients in 1954 with an error of 4.1%.[64] In addition to the usual clinical and laboratory procedure, the roentgen examination in all had been repeated at least once, and in 104 patients, both x-ray and gastroscopy had been repeated at least once; exfoliative cytology was employed infrequently. In a more recent series of 130 cases, observed from 1950 to 1958,[65] 104 were diagnosed unequivocally as benign and treated medically. Benign ulcers were demonstrated at operation in 18 patients. Three ulcers were diagnosed as malignant and were resected. Five of the one hundred thirty patients were treated temporarily but erroneously as benign, a diagnostic error of four

per cent. The studies had included roentgen examination, gastroscopy, gastric analysis, and examination of the stools for blood in most of the series; gastric cytology was utilized in 99 patients but encompassed the initial stages of the technique when the accuracy of the method was considerably less than at present (correct diagnoses have been made in 99 of the last consecutive 100 cases of benign gastric ulcer).

The survey of 307 patients by Doll, Jones, Pygott and Stubbe is noteworthy.[66] For 22 patients in whom the diagnosis was established initially at emergency gastric resection for hemorrhage or perforation, three years later diagnosis was unchanged. In 266 patients initially evaluated as having benign gastric ulcer by usual methods, carcinoma was found later in only one (0.4%); among 19 patients in whom a possible malignancy had not been excluded completely, carcinoma was diagnosed in 4 (21%). Two observations occasionally were helpful: achlorhydria despite administration of histamine—or pH values in the 12-hour secretion consistently exceeding 3.5—and the presence of a large ulcer at or distal to the angulus. Doll et al. conclude that "a benign gastric ulcer can be distinguished from a malignant ulcer with confidence in the great majority of cases and that the risk of misdiagnosis has not proved great enough to justify recourse to surgery as a routine treatment."

Clinical Observations.—The diagnostic approach to gastric ulcer requires detailed study of the patient in the hospital (with all procedures applied skillfully), careful analysis of the findings, and close supervision subsequently. There are no immediate criteria of benignancy.[4,67-70] Therefore, neither the roentgenologist nor the gastroscopist can be expected to establish the accurate diagnosis routinely at the first examination, though this, of course, is possible. The emphasis should be upon repeated studies, unless the initial observations are unequivocally diagnostic of malignancy. None of the methods (with the possible exceptions of exfoliative cytology and gastroscopic biopsy) provides immediate conclusive evidence, yet each may contribute useful information.

Clinically, the age and sex of the patient are not helpful. The history may be suggestive, but usually it is not decisive. Recurrence of the same distress for several years or longer and periodicity of the symptoms are infrequent in gastric cancer; however, the patient may have had an independent benign ulcer. The symptoms of a benign ulcer may be brief, and a long history of abdominal discomfort may be unrelated to the subsequent development of carcinoma—as in patients with both benign ulcer and gastric carcinoma.[71] The presence or absence of typical ulcer pain is not diagnostic because, in the presence of hydrochloric acid, gastric carcinoma may undergo peptic ulceration, activating the same pain mechanism as in benign ulcer. A change in the character of the symptoms or in the location or severity of the pain and its response to antacids are not decisive. Atypical distress, decreased appetite, and loss of weight occur in both gastric carcinoma and in benign ulcer, especially among older patients. Bleeding is slightly more frequent in benign than in malignant ulcer, but the difference is not distinctive. The physical examination does not necessarily facilitate the diagnosis; a "mass" may be palpated in benign gastric ulcer, and the examination often is normal in the presence of carcinoma.

Laboratory Observations.—The presence or absence of occult blood in the feces is not necessarily diagnostic. However, persistently negative stools suggest a benign ulcer, because at least 75% of gastric cancers bleed persistently. The disappearance of occult blood during therapy occurs both in healing benign ulcer and in the healing peptic ulceration of carcinoma. However, persistent occult blood in the feces during careful medical treatment (with the patient on a meat-free diet) is suggestive of malignancy and is an indication for operation.

Hydrochloric acid is demonstrable in all patients with benign gastric ulcer when secretory function is tested adequately; that

is, fluoroscopic confirmation of the proper position of the tip of the tube at the angulus of the stomach, stimulation with histamine or histalog, and measurement of pH.[72] The secretory pattern in gastric ulcer is not diagnostic, though the output of acid usually is normal or below normal; high values also occur in both benign and malignant lesions. The continued absence of hydrochloric acid or very low outputs despite adequate stimulation in the presence of an ulcer crater strongly suggests malignancy. Other occasionally helpful secretory indices are pH values consistently above 3.5 and combined measurements of the concentration of hydrogen and chloride ions in gastric juice after maximal stimulation with histamine.[74] Measurements of urinary pepsinogen may provide useful information.[75] Values of 1,000 units or less, in the presence of an ulcerating gastric lesion, increase the probability of carcinoma, since only 1% of 90 patients with gastric ulcer excreted less than 1,000 units. Values exceeding 3,000 units favor, but do not prove, the diagnosis of benign ulcer. These laboratory analyses provide information of relative value; however, their contribution to the total evidence may be important.

X-Ray Examination of Stomach.—The roentgen examination of the stomach remains the single most important method for the recognition of gastric ulcer, and it contributes significantly to the differential diagnosis. The value of the method is in proportion to the skill, experience, interest and facilities of the examiner, the cooperation of the patient, the index of suspicion of the clinician, and the opportunity for repetition of the examination during therapy. A careful study of the ulcer and the adjacent mucosa by fluoroscopy and mucosal relief views provides valuable information.[76] Most of the diagnostic errors involve infiltrating lesions (overlooked because of inexperience), inadequate technique, or diagnostically poor x-ray films[77]; suspicious evidence on the x-ray films often is not recognized, except in retrospect.

There is no single roentgen sign of benignancy.[78-80] Though most benign ulcers occur on the lesser curvature of the body of the stomach, location is not helpful in diagnosis. Benign and malignant ulcers may occur at any site; ulcers on the greater curvature often are malignant but occasionally are benign. A smooth, sharply defined ulcer crater, projecting from the lesser curvature beyond the natural outline of the stomach and with a perfectly regular collar, almost invariably denotes a benign lesion. Other roentgen features associated with benignancy include a sharp line or narrow band of translucency about the orifice of the crater, greater depth than width of the crater, smooth ulcer floor, and mucosal folds radiating to the very edge of the ulcer crater, without evidence of infiltration of the mucosa or the gastric wall.

The grossly irregular ulcer crater is highly suggestive of carcinoma, but there are exceptions. Other roentgen indications of malignancy include a flat, saucer-like crater with a base broader than the apex located within the confines of the gastric outline, rolled or rounded edges in contrast to the undermined border of the benign ulcer, rigidity or nodularity of the adjacent gastric wall, failure of peristalsis to traverse the ulcer area, and mucosal folds pointing toward the ulcer crater but not reaching it. The inflammation surrounding an inflamed or chronic callous benign ulcer may simulate neoplasm initially; however, repeat study frequently clarifies the problem. Large gastric ulcers often are benign,[21,22] small ulcers may be malignant. A decrease in the size of the crater roentgenologically does not necessarily indicate benignancy, for peptic ulceration in carcinoma also may heal (at least, partially) during antacid therapy. However, malignant ulcers very rarely heal completely; neoplastic infiltration of the wall at the site of the ulcer scar usually can be detected radiologically. Failure of the ulcer to decrease or disappear within two to three weeks does not necessarily denote malig-

nancy, nor does an increase in the size of the ulcer crater indicate neoplasm.[49]

Despite the limitations of the roentgen technique and the relative value of the information provided, the procedure is capable of an accuracy of 85% to 95%. Klotz, Kirsner, and Palmer [81] reported an accuracy of 88% in the diagnosis of 82 surgically proved gastric neoplasms and an accuracy of 79% in the diagnosis of 122 benign ulcers.

Gastroscopy.—According to Schindler,[82] gastroscopy is especially helpful in differential diagnosis because the blood circulating through the living tissue produces brilliant contrasts in color, facilitating the recognition of abnormal changes. Like x-ray, the value of the technique is dependent upon the experience and skill of the examiner as well as the cooperation of the patient. Similarly, gastroscopy cannot be expected to establish the correct diagnosis routinely at the first examination; accuracy increases with repetition.[83] Among 273 gastric ulcers studied by Schindler and Desneux,[84] 239 were diagnosed accurately (191 as benign and 48 as malignant); among 20 evaluated incorrectly, 18 diagnosed as malignant were benign and 2 diagnosed as benign were malignant; among 14 with indefinite classifications, 9 were benign and 5 malignant. The diagnostic error not only was low but it was chiefly in overdiagnosing rather than underdiagnosing malignancy. Perhaps the most important limitation of gastroscopy is the inability to visualize the entire stomach. Among 122 benign gastric ulcers, 96 were visualized but, with one exception, all were interpreted correctly.[81]

Gastroscopy is especially helpful in the study of ulcers on the lesser curvature of the stomach at or in proximity to the angulus. Under favorable circumstances, gastroscopic observation of the healing of the ulcer and the demonstration of a normal adjacent mucosa is almost always indicative of benignancy. Gastroscopically, the typical benign ulcer presents a clean, gray base; the margins are smooth and sharply defined; the surrounding mucosa is not irregular or nodular, and peristaltic activity is normal.[85] An associated gastritis may produce the appearance of rigidity or infiltration of the gastric wall, defying accurate diagnosis, but repeat examination during therapy permits the differentiation. Rugal folds radiate directly to the margin of the benign ulcer crater. The adjacent mucosa usually is smooth and pliable. The malignant ulcer is characterized by a brownish or dirty-gray base, irregular or nodular margin, induration and rigidity of the adjacent gastric wall, and blending of part or all of the ulcer margin into the surrounding mucosa. The mucosal folds are interrupted and disturbed; peristalsis in the ulcer area is decreased or absent. Biopsy of gastric lesions is possible with the "operating gastroscope" and seems useful in the hands of skilled examiners. In our experience, gastric biopsy facilitated the accurate diagnosis of carcinoma in one case; the method has been employed infrequently.

Exfoliative Cytologic Examination of the Stomach

Exfoliative cytology of the stomach probably is the most definitive procedure for differentiating benign and malignant ulcers clinically. The accuracy of the method rises in proportion to the interest, skill, thoroughness, and experience of the cytologic group and with repetition of the study. With proper training and supervision, intelligent technicians can become highly proficient in the procedure. The most effective technique in our laboratory for obtaining representative cellular material is vigorous, repeated lavage of the fasting stomach with isotonic saline solution.

Whereas the diagnostic accuracy of the method initially (in our experience) approximated 75% to 80%, since August, 1955, a correct cytological diagnosis has been made preoperatively in 145 of 154 patients (95%), eventually proved to have carcinoma or sarcoma of the stomach.[86] The

false-negative results were attributable to improper positioning of the gastric tube, inability to initially identify a few malignant cells, temporary re-epithelization of a malignant ulcer base (in two cases), and failure of a minute submucosal carcinoma to penetrate the surface; four of the false negatives were lymphomas. Benign gastric ulcer in the healing phase occasionally may exfoliate a large cell whose nucleus is increased in size and contains an increased amount of chromatin, resembling neoplasm; these variants now are recognized more readily. The presence of abnormal or unidentifiable cells in the gastric wash necessitates repeat examination with very vigorous lavage; the second wash almost always resolves the problem. In all cytologically positive cases, some malignant cells are found in the initial study; when the cells are few in number or not well preserved, the second lavage usually produces abundant neoplastic cells. In our experience, the negative cytologic study has become increasingly important. Of 1,054 patients with benign gastric disorders, only 4 (0.5%) were diagnosed erroneously as having malignancies (false-positive); pathological processes were found in the stomach or duodenum in each —in 3, duodenal ulcers, and in the 4th, multiple, shallow, healing ulcers of the lesser curvature of the stomach. In the last 100 consecutive cases of benign gastric ulcer, the cytologic examination was correct in 99; the single error was in the misinterpretation of actively regenerating cells. Thus, the negative gastric cytologic report has positive value, approaching the diagnostic significance of the positive cytological report.

Therapeutic Test.—The "therapeutic test" is perhaps the most decisive method of diagnosis in gastric ulcer.[87,88] It is justified only when the total evidence suggests a benign ulcer and when the patient can be observed continuously with frequent reexamination. The uncontrolled treatment of a nonhospitalized patient, inadequate medical management, failure to maintain therapy until the ulcer has healed completely, treatment in the presence of suspicious findings or despite insufficient improvement, and premature termination of medical management by gastric resection are not acceptable "therapeutic tests."

Some benign gastric ulcers heal within several weeks; others require several months.[89-91] The period of observation, thus, may be three, five, or eight weeks, provided the evidence continues to indicate benignancy; uncertainty as to the diagnosis is an indication for operation at any time. The assumption that gastric ulcers not healing within two or three weeks are malignant is incorrect. However, significant healing should occur within four to six weeks, with thorough medical treatment in the hospital; the crater should be considerably reduced in size within eight weeks. Little diagnostic reliance can be placed upon the subsidence of symptoms, gain in weight, or disappearance of occult blood from the feces. The important objective is complete and permanent healing, demonstrated by x-ray and gastroscopy and fortified by repeatedly negative gastric cytology. The patient subsequently should be restudied at intervals of 3, 6, and 12 months and then at longer intervals to document the permanency of the healing. Peptic ulceration in gastric cancer may heal temporarily during antacid therapy[37,67,92]—the regenerated epithelium consisting of normal or neoplastic cells[4]—but such cases are rare, and their importance as obstacles in differential diagnosis has been overemphasized. In the relatively few instances of apparently complete healing, symptoms rarely have disappeared completely; careful roentgen and gastroscopic study has revealed abnormal findings, such as nodularity, infiltration, or diminished peristaltic activity, incompatible with a benign ulcer.[4] The therapeutic test, properly performed, thus, is a most useful procedure, but it requires careful treatment and supervision as well as the complete cooperation of the patient. In the absence of these conditions, the therapeutic test probably should not be undertaken.

The Alleged Hazard of Neoplasia

The concept of carcinomatous transformation of benign ulcer appears to have developed by analogy with the neoplastic changes observed occasionally in areas of chronic inflammation and ulceration elsewhere in the body and upon the theoretical appeal of the sequence of ulceration and inflammation, regenerative hyperplasia, and unregulated neoplastic growth. The problem has been debated since Cruveilhier [93] suggested the possibility in 1893.[94] Early supporters of this theory included Rokitansky,[95] Zenker,[97] Hauser,[98] Finsterer,[99] Hurst,[101] and McCarty and Wilson,[102] among others. Early opponents of this view included Dittrich,[109] Tripier,[110] Duplant,[111] Saneroth,[112] Cabot and Adie,[94] Exalto,[113] Borrmann,[114] and Ewing.[115] Estimates of neoplasia in benign gastric ulcer range from 0 to 100%.[116] Beattie and Moroney [117] have indicated the inadequacies of the statistics and the hazards of reason by analogy. No one seems to have actually established histologically the benign nature of a gastric ulcer and then observed its transformation to carcinoma [68,69]; such evidence, admittedly, is very difficult (if not impossible) to obtain. Evaluation of the problem has been complicated further by the varying (often inadequate) criteria of malignancy in benign ulcer; by failure to recognize the atypical (but non-neoplastic) regenerative epithelial changes in healing benign ulcer as well as the changes produced by peptic digestion of gastric carcinoma, and by conflicting data as to the incidence of cancer of the stomach in patients with benign gastric ulcer. Conceding the possibility of neoplasia on a theoretical basis, the incidence must be extremely low, perhaps not exceeding 1 or 2%.

In the past, futile attempts have been made to characterize the theoretical transition of benign to malignant ulcer on the basis of clinical information, such as change in symptomatology, presence or absence of hydrochloric acid in the gastric content, or the development of carcinoma in the stomach previously containing an ulcer.[118] This *post hoc ergo propter hoc* type of reasoning is perhaps illustrated by the following:[119] "If there roentgenologically has been established an ulcer which healed after treatment, and which later recidivated in loco, and there subsequently at operation and patho-histological examination is found a chronic ulcer with cancer degeneration, this surely proves that the cancer has arisen secondarily on the basis of an ulcer." These are assumptions, not facts, and, therefore, unacceptable as scientific evidence. The finding of a carcinoma four or five years after a clinical impression may be suggestive. However, the clinical impression may have been incorrect; the lesion may have been a slow-growing carcinoma. Gastric cancers vary greatly in their biologic behavior [120]; some progress rapidly; others proceed at an amazingly slow rate, for three or five years or more.

There is no complete agreement, even among experienced pathologists, as to the precise histologic criteria of neoplasia in a benign gastric ulcer or that such a transition can be demonstrated microscopically.[29,38,115,117,121-123] The traditional histologic features of chronic benign ulceration include (*a*) complete destruction of the muscle at the base of ulcer; (*b*) an ulcer floor consisting of granulation and fibrous tissue, sometimes extending to the submucosa or to the serosa; (*c*) obliterating endarteritis at the base of the ulcer, and (*d*) fusion of the muscularis mucosae and muscularis propria at the edge of the ulcer.[94,104,124] Suggested criteria of malignancy in benign ulceration have included [94,115,125-127] carcinomatous proliferation in the margin, without involving the base or most of the periphery of the crater; neoplastic infiltration of the submucosa; a carcinomatous focus between the muscle ending in the edge of the ulcer and the overhanging mucosa, with invasion of the muscle; multicentric foci of carcinoma at the ulcer margin, extending into the submucosa and penetrating the free ends of the

muscle layer; carcinoma limited to the borders or surface of the ulcer, the neoplastic cells infiltrating the scar tissue and not connected with the normal glands at the border of the ulcer; changes in the staining qualities of nuclei, atypical mitotic figures, and infiltration of the neoplasm between the muscularis mucosae. None of these criteria apparently is absolutely diagnostic of neoplastic transformation of a benign ulcer, for ulceration of a primary carcinoma may produce all the changes hitherto ascribed to benign lesions. The presence of neoplastic cells in a portion of the wall of an otherwise benign-appearing gastric ulcer does not necessarily signify neoplastic transformation of an originally benign ulcer. The histologic evaluation of carcinomatous ulcers, except by the most experienced pathologists, may be difficult; Gomori [128] described three malignant ulcers with a fibrous base initially suggesting carcinoma *ex ulcere*, but on closer study, classified as primary carcinoma. We recently reviewed a gastric lesion interpreted by an expert pathologist in 1940 as adenocarcinoma but reevaluated in 1959 as lymphoma; the patient survives after 19 years, though leukemia has developed. The presence of neoplasm at the site of a previous ulcer also cannot be regarded as diagnostic. Hauser,[98] Borrmann,[114] Anschuetz and Konjetzny,[129] Klein,[122] and Bueerman [130] have described the independent occurrence of carcinoma and ulcer anatomically adjacent to one another and their subsequent fusion which creates the illusion of a carcinomatous ring in the margin of a chronic benign ulcer.

The bizarre, carcinoma-like, but nonneoplastic, epithelial hyperplasia at the margin of a healing benign ulcer is a potential source of confusion. Friedlander and Cohnheim,[131] in 1877, described such changes in response to chronic irritation. Wilensky and Thalhimer [121] demonstrated that removal of the irritation was followed promptly by regression and disappearance of the neoplastic-like findings. In exfoliative cytologic studies, we occasionally have observed bizarre cells simulating neoplasm in patients with benign ulcer, the cells disappearing after the ulcer has healed. The sequence of events has been described by Spilsbury. [132] As in chronic ulcerative processes elsewhere, healing is accompanied by active-cell proliferation. The cells increase in length, may become dilated, and assume an irregular arrangement. The gastric glands also extend for a variable distance upon the sides and base of the ulcer; the glands are short; their cells are arranged irregularly, rest directly upon the scar tissue, and present varying degrees of atypia. The majority of these glands probably atrophy and disappear as the supporting scar tissue contracts, reducing their blood supply and the area for their attachment. At this stage, there are commonly found, at the edge of the ulcer, gland cells which have penetrated deeply into the scar tissue and are cut off from regenerating glands. Lying deep among the fibers of the muscularis mucosae and in close proximity to the circular muscle, they may present an atypical glandular arrangement or may form narrow, solid columns of cells; isolated cells also are seen, and these cells, detached from the regenerating epithelium and buried in the fibrous tissue of the ulcer, sometimes are referred to as precancerous, or, from their position and irregular arrangement, are regarded erroneously as indicating malignant transformation in a benign ulcer. Ewing,[115] Wilensky and Thalhimer,[121] Klein,[122] and others have made similar observations. Dible [133] noted atypical regenerative hyperplastic changes in 32% of 125 ulcers and Newcomb,[134] in 29% of 161 chronic gastric ulcers. According to Gomori, the prepyloric area is especially prone to this response, producing irregular glands and polymorphic, deeply staining cells, difficult to distinguish from carcinoma. According to Spilsbury, if carcinoma develops in peptic ulcer, it must do so from extensively regenerating mucous membrane at the margin of a healing ulcer

or from buried epithelium. Such a carcinoma might spread from the margin into the base or into the normal gastric wall, a very rare sequence. The presence of displaced and buried epithelium is not peculiar to healing peptic ulcer and may be found in healing chronic ulcers of the skin and other mucous membranes. Similar hyperplastic changes have been noted in gastrojejunal ulcer by Wilensky and Thalhimer [121] who also caution that when the microscopic appearance of a chronic gastric ulcer is doubtful the atypical forms probably are hyperplastic and not malignant.

The tendency of gastric carcinoma to ulcerate has been known for many years. In 1907, Verse [135] described ulceration of a carcinoma with conversion of the base into dense cicatricial tissue resembling a benign ulcer. Stromeyer [136] suggested that the tumor might be digested completely. Gruber,[137] Moskowicz,[138] Billroth,[139] and Ziegler [140] later reported similar cases. Despite the theoretical objections of Hauser, and numerous other workers,[108-141] emphasizing the unlikelihood of symmetrical digestion of an entire tumor, the concept of peptic digestion of gastric carcinoma is firmly established.[4,142-144] Digestion may occur to the muscular layer or the serosa, leaving no trace of the tumor over most of all the base and only a peripheral ring of neoplastic cells. Superficial carcinomas apparently are susceptible to digestion by acid and pepsin.[145] Wilensky and Thalhimer [121] suggested the following sequence; minimal digestion producing a defect entirely surrounded by carcinoma in both the base and the periphery, moderate necrosis producing a lesion with the base free and the periphery containing carcinoma or with neoplasm in parts of the base and periphery, and near-maximal digestion producing a base entirely free of carcinoma and a periphery containing small fragments of tumor or in which differentiation between hyperplasia and malignancy is difficult. Because the focus of recognizable neoplasm is small, the erroneous assumption often is made that it must be of very recent origin and that the ulcer antedates the carcinoma. In the classic case of Wilensky and Thalhimer, all traces of an original carcinoma (apparently metastisizing to lymph nodes) had been completely excavated, with the regional lymph nodes containing carcinoma. As Mallory [142] and Palmer and Humphreys [143] have described, the lesion closely resembles or mimics benign ulcer; the features include complete destruction of an area of muscle corresponding in size to the floor of the ulcer, the presence of dense fibrous and granulation tissue covered by a necrotic layer, and indeed, fusion of the muscularis propria in the edge of the ulcer, hitherto regarded as pathognomonic of benign ulcer. While the four cases described by Palmer and Humphreys simulated a benign lesion, diagnostic signs of carcinoma were present. Klein [146] also has emphasized peptic digestion of carcinoma as a source of error in the histological evaluation. Among 141 patients with chronic gastric ulcer and 353 cases of carcinoma, only 2 instances of possible carcinoma in ulcer could be detected, and despite the use of the strictest criteria available, the transition was not regarded as unequivocally established. Mallory concludes: "It is evident that the greatest caution is necessary in attempting to interpret from the histologic picture the genesis of a malignant ulcer. Proof of the sequential relationship of ulceration and neoplastic development is extremely difficult in the individual case."

An increased frequency of gastric cancer often is assumed in patients with benign gastric ulcer.[12,50] Helsingen and Hillestad [147] reported 11 carcinomas in 229 patients, an average of 20 years after gastric resection for peptic ulcer, with a threefold higher incidence in the gastric ulcer group. Flood and Hennig encountered 5 instances of gastric carcinoma among 101 patients, 3 to 20 years after an original diagnosis of gastric ulcer. Cain et al.[148] reported 30 gastric carcinomas among 414 gastric ulcer patients treated medically.

According to Lew of the Society of Actuaries [149]: "For all of the classifications of gastric ulcer with operation, the mortality from all types of malignant neoplasms among insured persons reporting an operation for gastric ulcer was about 240 per cent of the normal, taken as that among persons insured at standard premium rates. This observation is based on 38 reported deaths from all types of malignant neoplasms. In the same classification there were 17 deaths from malignant neoplasms of the digestive system which was equivalent to about 275 per cent of the normal."

"In the classification of gastric ulcer without operation, there appeared to be no excess mortality from malignant neoplasm, as compared with that which would have been reported among persons insured at standard premium rates." A similar trend in mortality of insured persons operated upon for duodenal ulcer was noted.

In many surveys, the incidence of gastric cancer in patients with gastric ulcer is no higher than would be expected in the same age population without gastric ulcer. Nielsen [150] found no increased tendency to neoplasm among 155 patients with "unequivocal ulcer symptoms" for periods of 6 to 57 years and observed for 2.5 to 20 years. Bamberg [151] reported gastric carcinoma in 2.1% of 1,025 ulcer patients treated by gastroenterostomy and in 1.9% of 152 cases undergoing resection. In the lesions treated by gastroenterostomy only, and in which neoplasm was found later, the possibility arises that some of the ulcers were carcinoma, originally. Other data on the incidence of gastric cancer after gastroenterostomy for gastric ulcer include none in 80 cases observed up to 12 years,[152] one in 112 patients,[153] 2 in 208,[154] and none in 200 cases.[155] Brown [156] followed 77 of Sippy's original cases of gastric ulcer for 3 to 18 years and found gastric carcinoma in only one. Bachrach cites the follow-up of 332 patients treated medically, with only two instances of gastric carcinoma—6 and 23 years later. The incidence of gastric carcinoma was not increased in 78 patients with benign gastric ulcer treated medically and observed by us for 10 to 22 years.[64] Pack and Banner [157] recently reported no increased incidence of gastric carcinoma among persons with gastroenterostomy or resection for peptic ulcer. Côté, Dockerty, and Cain,[158] for the 50-year period from 1905 to 1954, noted only 17 instances of gastric carcinoma after operation for peptic ulcer and concluded that, "carcinoma of the stomach rarely develops in patients who have been treated either by resection or excision of the ulcer." Many patients with continuously or recurrently active gastric ulcer have been observed for long periods without development of carcinoma (Case 2). Thus, much of the available evidence indicates that gastric ulcer does not predispose excessively to gastric cancer.

Survival in Gastric Cancer

Biologic Characteristics of Gastric Carcinoma.—The routine removal of all gastric ulcers has been recommended as the only means of removing "early" carcinoma and improving the disappointing survival rate of gastric cancer. Supporters of this view cite the rise in five-year survival rates from 5% to 10% or 15% in recent years and especially the 35% to 45% survival after resection of ulcerating carcinomas simulating benign ulcer.[1,2,159-164] There is insufficient evidence at present to determine whether or not resection of all gastric ulcers will increase significantly the survival of gastric cancer. Involved in this question are considerations of operative mortality and postoperative morbidity as well as the quality of the medical and surgical care available to the patient, both in large medical centers and in small hospitals. The recent rise in five-year survival of gastric cancer cannot be ascribed exclusively to the removal of "early" cancer. Other factors, including improved surgical skill, better methods of anesthesia, improved pre- and postoperative care, chemotherapy, and more skillful use of electrolytes and fluids undoubtedly have contributed significantly to this trend.[165]

A survey of gastric cancer at the University of Chicago in 1948 indicated a five-year survival rate of 7.4%.[166] However, there were numerous deaths from pneumonia, peritonitis, other infections, and shock, in which autopsy demonstrated no residual carcinoma; if these cases had been saved by modern medical therapy, the five-year survival rate in this series (in 1948, at least) might have increased to 12% or 15%.

A more significant consideration is the biologic nature of gastric cancer. "Early" carcinoma is not necessarily synonymous with either the small size of the lesion or with brief duration of symptoms. Small cancers producing symptoms of only a few weeks' duration may cause death rapidly—the so-called "acute" carcinoma.[167] Other tumors, often characterized by prolonged symptoms and not operated upon for months or years, yet may be associated with prolonged survival after resection—the "chronic" carcinoma.[168,169] A third group of tumors, with an intermediate rate of growth, follows a "subacute" course. "Biological predeterminism," according to McDonald and Kotin,[170] rather than the time or type of surgical treatment, governs the end results in gastric carcinoma. Various attempts have been made to define the biologic features of gastric carcinoma, especially the tumors associated with long survival.[171-174] Black, Opler and Speer[172] emphasized sinus histiocytosis and/or a lympocytic reaction in the stroma of the primary tumor as more important than the age or sex of the patient, preoperative delay, gross or microscopic growth pattern, or the absence of metastases. In the Borrmann classification, based upon the gross appearance and extent of the tumor, the type I, well-demarcated polypoid (nonulcerating lesion) and the type II localized (ulcerating) dish-like lesion offer a much better prognosis than the type III, partially infiltrating, and type IV, diffusely invading, growths. Steiner et al.[175] found survival in gastric cancer associated with (1) sharp circumscription and growth of the tumor en bloc; (2) retrogressive changes consisting of cell atrophy, nuclear pyknosis, and cell degeneration at the margin of the tumor or distributed diffusely, and (3) two special histologic cell types, an undifferentiated medullary, and small-celled carcinoma. These factors appeared more reliable than histologic grading, macroscopic typing, or a combination of these. The survival of patients with demonstrable metastases in regional lymph nodes was noteworthy in this series. Regardless of the criteria employed, survival in gastric carcinoma is not entirely a matter of "early" diagnosis or surgical skill, important as these factors are, but also involves the biological growth rate of the carcinoma and the resistance of the individual patient to the tumor (Case 3).[176,177] Routine resection of all gastric ulcers as a means of improving cancer survival, therefore, can be justified only if surgery has no mortality and no significant morbidity.

Treatment

The medical management of gastric ulcer, as in duodenal ulcer, depends essentially upon the effective decrease or elimination of hydrochloric acid from the gastric content.[178] Regardless of other possible etiologic factors, all benign ulcers would heal completely if the acid were abolished. Unfortunately, this objective is difficult to attain. Nevertheless, nearly all uncomplicated gastric ulcers respond to therapy emphasizing maintenance of the general health of the patient; adequate rest; relief from physical and emotional tensions; avoidance of gastric irritants in food, drink, or medication; adequate neutralization of the acidity; effective use of gastric antisecretory drugs, and sedation. Since the rate of healing of benign ulcers varies, the length of intensive treatment is determined for the individual case. The success of the program depends upon the patient, the "life situation," other diseases present, certain complications (such as gastric retention or chronic perforation of the ulcer into the capsule of the pancreas or liver), and finally, the skill and perseverance of the physician. Small, relatively acute ulcers heal rapidly, and chronic callous

ulcers heal slowly. However, large craters may decrease and disappear at a surprisingly rapid rate. In a series of 104 patients with gastric ulcer, approximately 37% healed within six weeks; 43%, during periods up to four months, and in 20%, four or more months were required for complete healing.[64] While the immediate response to medical management generally is favorable, the long-term results are less satisfactory.[17] In various surveys, the proportion of sustained beneficial effects ranges from only 20% to 50%.[180-183] Recurrences and complications are common, and surgery becomes necessary for an increasing number of patients. Johnsson, Lindholn, and Stenstrom [184] reported sustained benefit in 44% of 219 cases observed between 1930 and 1945. Treatment had consisted of diet; an antacid mixture of magnesium subcarbonate, bismuth subsalicylate, and belladonna extract was given three times daily, and a combination of Carlsbad salt, sodium bicarbonate, and sodium bromide was given twice daily. A regular diet was resumed after several months, except during the spring and fall. Of 231 patients treated medically, only 33% were controlled for five years, and 42% later required surgery. Flood and Hennig [185] reported recurrences in 99 of 101 patients observed an average of 5.6 years. The initial treatment in the hospital for most cases had included bland foods, milk and cream, alkalis, sedatives, and occasionally antispasmodics. Subsequently, "most patients modified their own diets within a few months, provided they felt well." Of 414 patients described by Cain et al.,[148] symptoms were relieved completely in only 85 patients and partially in 71 patients; therapy was directed by numerous physicians and presumably varied considerably. Only 20% of 135 patients reported by Dworken and his colleagues [186] obtained sustained benefit; symptoms recurred for less than one month each year in 25%, for longer periods in 40%, and surgery was required later in 15%. Therapy initially had included hospitalization, hourly milk and cream and antacids, bland diet, anticholinergic drugs, and sedatives; after hospitalization, treatment was directed by the individual patient's physician. The importance of continued, uniform supervision is perhaps indicated by Miller and Berkowitz,[187] reporting satisfactory results in 62% of 729 clinic patients with peptic ulcer and in 92% of 300 private patients.

Although poor general health of the patient, delayed gastric emptying, penetration of the ulcer into the pancreas, and other complications account for many of the medical failures, an important cause is the inadequacy of the treatment prescribed.[126] Too often, therapy consists merely in occasional doses of weak antacids after meals and admonitions to "watch your diet" and "take it easy." The requirements of a truly effective medical program for gastric ulcer are stringent; namely, hospitalization, adaptation of treatment to individual needs (especially in the selection and dosage of antacids), antisecretory drugs and sedatives, skillful management of the emotional problems of the patient, maintenance of intensive therapy until the ulcer has healed completely (by gastroscopy as well as by x-ray), and careful prolonged supervision of the patient after discharge from the hospital (Cases 4 and 5). Unless these conditions are met, the results of therapy will be erratic, and recurrences will be frequent. In addition to the inadequacies of the recommended program, practical difficulties arise (as emphasized by Banks and Zetzel [188]); economic problems or poor cooperation may interfere with comprehensive therapy. Patients tire of the diet, frequent feedings, antacids, and other medication and follow the program with varying degrees of faithfulness. The tendency of ulcer patients (when symptoms have subsided) to discontinue medication and to disregard other recommendations, without informing the physician, is well recognized. In uncooperative cases or situations preventing adequate medical supervision, surgical management may appear to be the more practical expedient.

As in duodenal ulcer, recurrences in gastric ulcer are not correlated with any single cause; the factors involved often are not apparent. The circumstances usually emphasized include physical and emotional stress, intercurrent illness, dietary indiscretions, and the ingestion of ulcerogenic drugs such as salicylates, adrenal steroids, or phenylbutazone (Butazolidin). The recurrence may be at the site of the previous ulcer or in a new location. There are no completely protective measures against recurrences, except the development of permanent anacidity. However, their frequency and severity can be decreased with an adequate, sustained medical program.

There are many favorable reports on the long-term results of medical treatment of gastric ulcer.[189,190] Of 47 patients who bled from a benign gastric ulcer, only 3 bled again during the following four to eight years.[191] Smith, Boles, and Jordan[56] observed 195 patients for more than five years; 73% of the latter group were free of symptoms. In a series of 116 patients observed between 1937 and 1954 and treated with mild gastric radiation to the acid-secreting portion of the stomach (in addition to standard therapy), the incidence of complications was reduced from 43% to 14%.[64] The results were favorable in 80 patients (69%); the ulcer failed to heal in 8 (7%), and failure due to recurrences was noted in 28 (24%); 30 of the 116 patients (26%) eventually came to surgery. The recent survey of a larger series (233 patients), treated similarly and followed to 1958, indicated recurrences in only 71 (30.5%); only 49 (21%) required surgery.[192] Mild roentgen irradiation to the stomach, in our experience, has been a useful adjunct to medical management. The beneficial effects are related to the decrease or total elimination of hydrochloric acid. The development of achlorhydria always results in complete healing of the ulcer without recurrence for the duration of the antisecretory effect (Case 6). Recurrences after irradiation always are preceded by the reappearance of hydrochloric acid. Acid returns at variable intervals in almost all cases, but in those with persistently lowered secretion, the subsequent clinical course has seemed less severe. There have been no important untoward effects, and the incidence of carcinoma in the irradiated group has not exceeded the incidence in the general population. Thus, effective medical management is capable of controlling up to 75% of all benign gastric ulcers. Medical treatment obviously is not perfect, and more effective methods of therapy are necessary. Nevertheless, the limitations of medical treatment do not justify routine surgical intervention.[123]

Surgery is indicated for ulcers not responding or recurring despite adequate treatment, for inability to exclude malignancy completely, for uncontrollable or recurrent bleeding, for ulcers associated with delayed gastric emptying, for those resulting from pyloric stenosis, for contraction of the lesser curvature or narrowing of the antrum, for ulcers on the greater curvature (recognizing that some are benign), and for acute or chronic perforation. Contraindications to operation are extreme old age, associated serious illness greatly increasing the surgical risk, and probably the ulcers or ulcer recurrences associated with the ingestion of ulcerogenic drugs.

The results of gastric resection for gastric ulcer are favorable in 85% to 95% of cases.[162,193-199] In the hands of skilled, specialized surgeons, the mortality rate approximates 1% to 3% and infrequently exceeds 5%. In hospitals, lacking the advantages of large medical centers, and in the hands of the "occasional" gastric surgeon, the mortality rate may not be as favorable. Despite increasing surgical skill and the concomitant therapeutic improvements, gastric resection is a serious (at times, fatal) operation (Cases 7, 8).

Physiological and nutritional disturbances after gastric resection occur in perhaps 10% to 15% of cases and are not inconsequential.[200-204] In one series, 46% of the patients who had had 70% or larger gastric resections for benign gastric ulcer noted

significant undesirable symptoms.[49] The principal problems are the dumping syndrome, anemia, vitamin deficiencies, steatorrhea, inability to gain weight, diarrhea, and mechanical obstruction at the site of anastomosis. In individual cases, the postoperative difficulties may be as disabling or, indeed, worse than the ulcer (Case 9). Jejunal ulcer is rare, though it may occur (Case 10).[206] Schindler[207] has emphasized the severe gastritis of the postoperative stomach. Since the postsurgical problems appear to be correlated with the magnitude of the resection, less extensive operative procedures have been recommended, including local excision of the ulcer[45] with vagotomy and gastroenterostomy or pyloroplasty,[208] hemigastrectomy, and antral resection with vagotomy.[45]

Comment

The total evidence, in our judgment, indicates that gastric ulcer is not an exclusively surgical problem. The differential diagnosis between benign and malignant ulcer can be established with an accuracy of 96% to 98%, provided all diagnostic methods are utilized (including gastroscopy and gastric cytology), provided the techniques are applied by skilled, experienced examiners and are repeated in doubtful cases, and provided there is opportunity for close supervision of the patient. The "therapeutic test" is an important component of the diagnostic approach, justifiable only when the entire evidence indicates a benign ulcer. The therapeutic test necessitates careful medical management in the hospital and repeated examination of the patient until the ulcer has healed completely, by gastroscopy as well as by x-ray, and the cytologic study remains negative. Under these circumstances, the diagnostic error should not exceed the mortality of expert gastric resection, and the possibility of postresection physiologic problems thereby should be obviated in many cases. The discouraging diagnostic reports in the literature are difficult to evaluate because important details of the diagnostic approach are lacking. Frequently, the methods of study appeared to be inadequate. Appropriate facilities may have been lacking; certain techniques may not have been available; the physician may not have had sufficient knowledge or interest in the problem. Poor cooperation of the patient in the diagnostic study or therapeutic test also may have suggested surgery as more practical therapy. These problems are understandable; skilled gastric resection probably is preferable to inept diagnostic study or inadequate medical treatment.

In the absence of conclusive data for the alleged carcinomatous transformation of benign ulcer, the theoretical hazard of neoplasia is not a satisfactory basis for the routine resection of gastric ulcer. Furthermore, there is no convincing evidence, as yet, that the resection of all gastric ulcers will improve the survival of gastric cancer. The removal of every stomach would accomplish this otherwise worthy objective, but it would accelerate the mortality from gastrectomy, and such a proposal obviously would be absurd. "Early" diagnosis is important, but it is not necessarily equated with the small size of the lesion or with the shortness of the interval between the roentgen recognition of a gastric ulcer and its removal. "Early" gastric cancer is a biological characterization, measurable in part by the relatively slow rate of growth of the tumor and by the lack of tendency to extension. This biologic concept cannot be utilized to justify complacency or delay in diagnosis and treatment; however, in attempting to evaluate this problem scientifically, the significance of the biologic concept should not be disregarded.

The medical treatment of gastric ulcer is more effective than has been publicized. The poor results in many instances can be ascribed to inadequate therapy, lack of cooperation from the patient, and lack of supervision of the program. When adequate treatment can be maintained, the immediate results are good and the long-term results are favorable in at least 50% or more of patients. The adjunct use of mild gastric

irradiation to decrease or abolish acid secretion appears to improve the results, with a favorable response in 60% to 75% of cases. Nevertheless, medical management is not completely satisfactory, and more effective methods or therapy (relating to the control of acid production and the resistance of the gastric mucosa) are desirable. Surgical treatment, preferably gastric resection, is required in 25% to 50% of patients with gastric ulcer because of lack of response to medical management, inability to exclude malignancy completely, and various complications. While the results of gastric resection are good and the mortality of the operation is relatively low, the procedure is not without serious hazard, and the physiologic and nutritional consequences of gastric resection are not inconsequential.

Thus, gastric ulcer is not a 100% indication for surgery. The problem of management can be dealt with effectively on an individual basis, provided thorough diagnostic study and careful medical management are undertaken, reserving for surgery the diagnostic problems and the complicated cases. The combined medical and surgical approach, applied judiciously and carefully, would appear to be the most justifiable approach to the problem of gastric ulcer at the present time.

Conclusions

1. Accurate differential diagnosis of benign and malignant gastric ulcer is possible in 96% to 98% of cases.

2. There is no conclusive evidence for the neoplastic transformation of benign gastric ulcers; the possibility is conceded, theoretically, in 1% or 2% of cases.

3. Survival in gastric cancer is determine by improved medical and surgical treatment, early diagnosis, and by the biologic nature of the tumor. There is no conclusive evidence, as yet, that the routine resection of gastric ulcers will improve survival of gastric cancer patients significantly.

4. Thorough sustained medical management is effective in up to 75% of uncomplicated benign gastric ulcers.

5. Gastric resection is an effective procedure for gastric ulcer in the presence of complications, uncertainty in diagnosis, and lack of sustained response to medical treatment.

6. Gastric ulcer is not a 100% surgical problem; it can be dealt with effectively on an individual basis.

CASE 1.—*Spontaneous Achlorhydria: Complete, Prolonged Healing of Gastric Ulcer.*

A 63-year-old housewife, who was first seen in 1937, had experienced ulcer symptoms since February, 1936. The past history included drainage of the gallbladder in 1912 and a cholecystectomy in 1925; a "tumor" of the stomach was reported to have been removed also. Gastric analysis revealed moderate amounts of HCl, with a maximum concentration of 74 units after histamine. Gastroduodenal x-rays in January, 1937, demonstrated a huge ulcer crater, 2.5 cm. in diameter and 2.5 cm. deep, projecting from the midportion of the lower curvature of the stomach above the angulus. Gastroscopy demonstrated a large, benign ulcer crater. Serial x-rays and gastroscopies demonstrated the gradual diminution of the ulcer, with complete healing in April, 1937. Between 1937 and 1949 the patient underwent many additional x-ray examinations, more than 65 gastroscopies, and numerous gastric analyses. Medical treatment consisted of bland foods, various antacids, and sedatives. Hydrochloric acid was always demonstrable in the gastric content. The ulcer nearly always was visualized at gastroscopy and often at x-ray, the size of the crater varying from time to time, but occasionally disappeared completely. In June, 1942, the patient spontaneously developed complete achlorhydria. Antacid therapy was discontinued. The ulcer healed and has not recurred. In March, 1959, the patient reported that, at the age of 85 years, she is free of ulcer distress and is very well.

Comment: This remarkable case is of interest for several reasons; the correlation of ulcer activity with acid gastric secretion, the permanent healing of the ulcer during 17 years of complete achlorhydria, and the excellent health of the patient 23 years after onset of the gastric ulcer.

CASE 2.—*Recurrent Gastric Ulceration 28 Years —No Carcinoma.*

A 46-year-old man had been treated for a gastric ulcer, demonstrated by x-ray, in 1922. In 1927, he had undergone an unknown type of operation elsewhere for recurrent gastric ulcer. Ulcer symptoms recurred in 1928; the patient was first seen at the University of Chicago in 1936. Between 1936 and 1950 he had at least 70 gastro-

duodenal x-rays and more than 125 gastroscopies, observing the course of a continuously active benign gastric ulcer on the lesser curvature of the stomach immediately proximal to the angulus. Therapy included numerous hospitalizations, a bland diet, calcium carbonate, various antisecretory drugs, and several courses of gastric radiation in an unsuccessful effort to lower gastric acidity. Many gastric analyses demonstrated moderate amounts of hydrochloric acid continuously. In July, 1949, the gastric ulcer was resected locally and a pyloroplasty established. The occurrence of retention necessitated a subtotal gastric resection in October, 1950. Histologic examination demonstrated a benign ulcer with dense scarring and an associated severe atrophic gastritis. The patient developed a subacute pancreatitis in 1956 and died of a coronary occlusion in 1957.

Comment: Gastric carcinoma did not develop despite recurrent gastric ulceration for 28 years and a persistently active large gastric ulcer for at least 14 years of close observation. This case also illustrates the difficulty in controlling gastric acidity in some patients and the resultant poor response to medical management.

CASE 3.—*Seventeen-Year Survival After Resection for Gastric Cancer and Four-Year Delay in Surgery.*

A 47-year-old woman, who was first seen in 1935, had experienced vague digestive symptoms since November, 1934; however, the appetite was good and there was no weight loss. The problem was interpreted as an irritable bowel and treated accordingly. The patient reappeared in 1938 because of postprandial and nocturnal epigastric and back pain of six months' duration. Gastroduodenal x-rays disclosed an ulcer on the lesser curvature of the stomach near the angulus; the evaluation was equivocal. Gastroscopy also visualized the lesion and a possible malignancy was suggested. Hydrochloric acid was present in the gastric content. The feces contained occult blood. Antacid therapy was instituted with varying symptomatic response. The ulcer never healed. Many roentgen and gastroscopic examinations and repeated clinical evaluations resulted in fluctuating diagnoses. Operation was recommended repeatedly in 1939, 1940, and 1941 and repeatedly refused by the patient. Surgery finally was undertaken in 1942, after 16 x-ray studies and 24 gastroscopies. A subtotal gastric resection was performed with the removal of a 2 × 1-cm. ulcer on the lesser curvature 7 cm. proximal to the pylorus; a colloid carcinoma involved part of the ulcer. The patient recovered uneventfully. In 1959, at the age of 72, she remains well.

Comment: The sequence of events in this case indicates the probable existence of an ulcerating gastric carcinoma since 1938 at least, and possibly 1934. Surgery, after four years of unintentional delay, appears to have been completely successful. The patient is well, 17 years after gastric resection and at least 20 years after the lesion was first recognized. It would appear justifiable to classify the tumor as a slow-growing, "chronic" carcinoma. Delay in definitive diagnosis and therapy appears not to have influenced the prognosis adversely.

CASE 4.—*Importance of Individualized, Intensive Medical Treatment.*

A white woman was 29 years of age when first seen in 1954, for nausea. Gastrointestinal x-rays and gastric cytology were normal. Gastroscopy disclosed slight atrophy of the stomach. Gastric analysis indicated no acid in the basal secretion and a maximum of 49 clinical units after the injection of Histalog. In January, 1955, she was hospitalized because of nausea and epigastric pain. The feces gave 4+ reactions for occult blood by the benzidine test. Gastroduodenal x-rays demonstrated an ulcer, 2 cm. in diameter and 1.5 cm. in depth, on the lower part of the lesser curvature—"almost certainly benign." Gastroscopy demonstrated the ulcer immediately proximal to the angulus, interpreted as benign. Therapy, in addition to bed rest and bland foods, included calcium carbonate 2.0 gm. alternating with 90 cc. of milk and cream every half hour and methscopolamine (Pamine) in daily doses up to 32.5 mg. daily. The milk and cream were given every two hours during the night, but the pain persisted. Beginning on March 23, a constant intragastric drip containing 10 gm. sodium bicarbonate per liter of milk was administrated each night, and for the first time, symptoms were relieved completely. After six weeks, the ulcer crater was slightly smaller; occult blood in the feces persisted. Calcium carbonate was continued in doses of 30 to 40 gm. daily without alteration in the serum electrolytes. Gastric irradiation therapy, 1,650 r, was administered from February 21 to March 3. Gastric analysis had revealed small amounts of acid in the basal secretion and up to 91 clinical units after Histalog. Six weeks after irradiation the maximal acidity was 20 units; the ulcer crater was much smaller on x-ray. Achlorhydria was demonstrated approximately nine weeks later; the ulcer crater now was so small as to be hardly identifiable. The intragastric drip was discontinued on April 7. Gastric cytology prior to discharge from the hospital again was negative. On May 19, 1955, gastroduodenal x-rays were normal. Gastric analysis in October,

irradiation to decrease or abolish acid secretion appears to improve the results, with a favorable response in 60% to 75% of cases. Nevertheless, medical management is not completely satisfactory, and more effective methods or therapy (relating to the control of acid production and the resistance of the gastric mucosa) are desirable. Surgical treatment, preferably gastric resection, is required in 25% to 50% of patients with gastric ulcer because of lack of response to medical management, inability to exclude malignancy completely, and various complications. While the results of gastric resection are good and the mortality of the operation is relatively low, the procedure is not without serious hazard, and the physiologic and nutritional consequences of gastric resection are not inconsequential.

Thus, gastric ulcer is not a 100% indication for surgery. The problem of management can be dealt with effectively on an individual basis, provided thorough diagnostic study and careful medical management are undertaken, reserving for surgery the diagnostic problems and the complicated cases. The combined medical and surgical approach, applied judiciously and carefully, would appear to be the most justifiable approach to the problem of gastric ulcer at the present time.

Conclusions

1. Accurate differential diagnosis of benign and malignant gastric ulcer is possible in 96% to 98% of cases.

2. There is no conclusive evidence for the neoplastic transformation of benign gastric ulcers; the possibility is conceded, theoretically, in 1% or 2% of cases.

3. Survival in gastric cancer is determine by improved medical and surgical treatment, early diagnosis, and by the biologic nature of the tumor. There is no conclusive evidence, as yet, that the routine resection of gastric ulcers will improve survival of gastric cancer patients significantly.

4. Thorough sustained medical management is effective in up to 75% of uncomplicated benign gastric ulcers.

5. Gastric resection is an effective procedure for gastric ulcer in the presence of complications, uncertainty in diagnosis, and lack of sustained response to medical treatment.

6. Gastric ulcer is not a 100% surgical problem; it can be dealt with effectively on an individual basis.

CASE 1.—*Spontaneous Achlorhydria: Complete, Prolonged Healing of Gastric Ulcer.*

A 63-year-old housewife, who was first seen in 1937, had experienced ulcer symptoms since February, 1936. The past history included drainage of the gallbladder in 1912 and a cholecystectomy in 1925; a "tumor" of the stomach was reported to have been removed also. Gastric analysis revealed moderate amounts of HCl, with a maximum concentration of 74 units after histamine. Gastroduodenal x-rays in January, 1937, demonstrated a huge ulcer crater, 2.5 cm. in diameter and 2.5 cm. deep, projecting from the midportion of the lower curvature of the stomach above the angulus. Gastroscopy demonstrated a large, benign ulcer crater. Serial x-rays and gastroscopies demonstrated the gradual diminution of the ulcer, with complete healing in April, 1937. Between 1937 and 1949 the patient underwent many additional x-ray examinations, more than 65 gastroscopies, and numerous gastric analyses. Medical treatment consisted of bland foods, various antacids, and sedatives. Hydrochloric acid was always demonstrable in the gastric content. The ulcer nearly always was visualized at gastroscopy and often at x-ray, the size of the crater varying from time to time, but occasionally disappeared completely. In June, 1942, the patient spontaneously developed complete achlorhydria. Antacid therapy was discontinued. The ulcer healed and has not recurred. In March, 1959, the patient reported that, at the age of 85 years, she is free of ulcer distress and is very well.

Comment: This remarkable case is of interest for several reasons; the correlation of ulcer activity with acid gastric secretion, the permanent healing of the ulcer during 17 years of complete achlorhydria, and the excellent health of the patient 23 years after onset of the gastric ulcer.

CASE 2.—*Recurrent Gastric Ulceration 28 Years —No Carcinoma.*

A 46-year-old man had been treated for a gastric ulcer, demonstrated by x-ray, in 1922. In 1927, he had undergone an unknown type of operation elsewhere for recurrent gastric ulcer. Ulcer symptoms recurred in 1928; the patient was first seen at the University of Chicago in 1936. Between 1936 and 1950 he had at least 70 gastro-

duodenal x-rays and more than 125 gastroscopies, observing the course of a continuously active benign gastric ulcer on the lesser curvature of the stomach immediately proximal to the angulus. Therapy included numerous hospitalizations, a bland diet, calcium carbonate, various antisecretory drugs, and several courses of gastric radiation in an unsuccessful effort to lower gastric acidity. Many gastric analyses demonstrated moderate amounts of hydrochloric acid continuously. In July, 1949, the gastric ulcer was resected locally and a pyloroplasty established. The occurrence of retention necessitated a subtotal gastric resection in October, 1950. Histologic examination demonstrated a benign ulcer with dense scarring and an associated severe atrophic gastritis. The patient developed a subacute pancreatitis in 1956 and died of a coronary occlusion in 1957.

Comment: Gastric carcinoma did not develop despite recurrent gastric ulceration for 28 years and a persistently active large gastric ulcer for at least 14 years of close observation. This case also illustrates the difficulty in controlling gastric acidity in some patients and the resultant poor response to medical management.

CASE 3.—*Seventeen-Year Survival After Resection for Gastric Cancer and Four-Year Delay in Surgery.*

A 47-year-old woman, who was first seen in 1935, had experienced vague digestive symptoms since November, 1934; however, the appetite was good and there was no weight loss. The problem was interpreted as an irritable bowel and treated accordingly. The patient reappeared in 1938 because of postprandial and nocturnal epigastric and back pain of six months' duration. Gastroduodenal x-rays disclosed an ulcer on the lesser curvature of the stomach near the angulus; the evaluation was equivocal. Gastroscopy also visualized the lesion and a possible malignancy was suggested. Hydrochloric acid was present in the gastric content. The feces contained occult blood. Antacid therapy was instituted with varying symptomatic response. The ulcer never healed. Many roentgen and gastroscopic examinations and repeated clinical evaluations resulted in fluctuating diagnoses. Operation was recommended repeatedly in 1939, 1940, and 1941 and repeatedly refused by the patient. Surgery finally was undertaken in 1942, after 16 x-ray studies and 24 gastroscopies. A subtotal gastric resection was performed with the removal of a 2 × 1-cm. ulcer on the lesser curvature 7 cm. proximal to the pylorus; a colloid carcinoma involved part of the ulcer. The patient recovered uneventfully. In 1959, at the age of 72, she remains well.

Comment: The sequence of events in this case indicates the probable existence of an ulcerating gastric carcinoma since 1938 at least, and possibly 1934. Surgery, after four years of unintentional delay, appears to have been completely successful. The patient is well, 17 years after gastric resection and at least 20 years after the lesion was first recognized. It would appear justifiable to classify the tumor as a slow-growing, "chronic" carcinoma. Delay in definitive diagnosis and therapy appears not to have influenced the prognosis adversely.

CASE 4.—*Importance of Individualized, Intensive Medical Treatment.*

A white woman was 29 years of age when first seen in 1954, for nausea. Gastrointestinal x-rays and gastric cytology were normal. Gastroscopy disclosed slight atrophy of the stomach. Gastric analysis indicated no acid in the basal secretion and a maximum of 49 clinical units after the injection of Histalog. In January, 1955, she was hospitalized because of nausea and epigastric pain. The feces gave 4+ reactions for occult blood by the benzidine test. Gastroduodenal x-rays demonstrated an ulcer, 2 cm. in diameter and 1.5 cm. in depth, on the lower part of the lesser curvature—"almost certainly benign." Gastroscopy demonstrated the ulcer immediately proximal to the angulus, interpreted as benign. Therapy, in addition to bed rest and bland foods, included calcium carbonate 2.0 gm. alternating with 90 cc. of milk and cream every half hour and methscopolamine (Pamine) in daily doses up to 32.5 mg. daily. The milk and cream were given every two hours during the night, but the pain persisted. Beginning on March 23, a constant intragastric drip containing 10 gm. sodium bicarbonate per liter of milk was administrated each night, and for the first time, symptoms were relieved completely. After six weeks, the ulcer crater was slightly smaller; occult blood in the feces persisted. Calcium carbonate was continued in doses of 30 to 40 gm. daily without alteration in the serum electrolytes. Gastric irradiation therapy, 1,650 r, was administered from February 21 to March 3. Gastric analysis had revealed small amounts of acid in the basal secretion and up to 91 clinical units after Histalog. Six weeks after irradiation the maximal acidity was 20 units; the ulcer crater was much smaller on x-ray. Achlorhydria was demonstrated approximately nine weeks later; the ulcer crater now was so small as to be hardly identifiable. The intragastric drip was discontinued on April 7. Gastric cytology prior to discharge from the hospital again was negative. On May 19, 1955, gastroduodenal x-rays were normal. Gastric analysis in October,

1956, indicated a partial return of acid secretion after the injection of Histalog. The patient has remained well, and five x-rays subsequent to January, 1959, have been normal. Therapy consists of a liberal bland diet and small amounts of calcium carbonate, methscopolamine, and phenobarbital daily. She recently has delivered her fourth child.

Comment: This case illustrates the difficulty in controlling the acid gastric secretion in some patients with gastric ulcer; the importance of modifying the program to individual requirements, and the value of an intensive sustained medical regimen. "Standard" medical treatment was completely inadequate. She was 5′ 7″ tall, tense and nervous in temperament, and a likely candidate for the postresection dumping syndrome and the associated nutritional difficulties; fortunately, the excellent response to intensive medical management has obviated the need for surgery.

CASE 5.—*Sustained Response to Medical Management.*

A 39-year-old housewife had experienced epigastric pain radiating to the chest in November, 1953, but gastroduodenal x-rays appeared normal. Symptoms recurred, and after 10 months of ulcer-type distress, the patient was hospitalized. Tenderness was elicited in the midepigastrium. The feces were positive for occult blood. Moderate amounts of hydrochloric acid were present in the gastric content. X-rays demonstrated a large, benign-appearing ulcer crater in the midportion of the lesser curvature of the stomach; the duodenal bulb was slightly deformed. Gastroscopy disclosed a benign ulcer crater approximately 1.5 cm. in diameter on the lesser curvature at the angulus. Treatment included bed rest, bland foods, hourly calcium carbonate, methscopolamine, and sedatives. Gastric irradiation was administered between September 22, and October 2, 1954. Acid secretion decreased to near-achlorhydria levels. The symptoms were relieved completely. Roentgen and gastroscopic examinations at approximately monthly intervals demonstrated complete healing of the ulcer crater with striking demonstration of radiating folds traceable to the center of the ulcer crater. The patient remains well on a program of liberal bland diet, methscopolamine, and four to six teaspoons of calcium carbonate daily. Gastroduodenal x-rays in March, 1959, demonstrated a small scar pocket with radiating folds at the site of the previous ulcer.

Comment: The excellent response in this case has been sustained for approximately five years; a moderate diet and antacid therapy have been maintained continuously.

CASE 6.—*Prolonged Active Gastric Ulcer—X-Ray-Induced Achlorhydria, Prolonged Complete Healing.*

A 63-year-old white woman who was first seen in April, 1936, had complained of periodic ulcer distress radiating to the back for 30 years. There had been some weight loss. Physical examination revealed tenderness in epigastrium. Gastroduodenal x-rays disclosed a benign appearing gastric ulcer high on the lesser curvature of the stomach. Gastroscopically, the ulcer appeared benign and was associated with superficial erosions. Treatment with milk, antacids, and diet was followed by a remission of symptoms until September, 1936. X-rays in May and July had indicated healing with scar formation, but in October, 1936, an ulcer again was demonstrated on the posterior wall of the lesser curvature. Innumerable gastroscopies, often at monthly intervals, demonstrated the course of the ulcer as it fluctuated in size, healing and recurring from time to time, generally in relation to the carefulness with which the patient adhered to treatment. X-rays and gastroscopy in April, 1937, indicated almost complete healing of the ulcer, but in May and December, 1937, the ulcer was noted at gastroscopy again, although x-rays failed to visualize the lesion. In March, 1938, both x-ray and gastroscopy were reported as negative.

In July, 1938, symptoms had recurred; both x-rays and gastroscopy demonstrated gastric ulcer. She continued on a more careful regimen, with partial relief. In March, 1939, gastroscopy again revealed the chronic ulcer. Hospitalization was required again from Oct. 18, 1939, to Feb. 11, 1939, because of severe ulcer pain and vomiting. A severe alkalosis responded to fluid and electrolyte therapy. Gastroscopic examinations demonstrated a healing gastric ulcer with scar formation. X-rays indicated a pronounced decrease in size of the ulcer with converging scar pattern. During the next seven years, the pattern of recurrence and healing was noted repeatedly. Although x-rays did not demonstrate the ulcer consistently, the lesion was almost always visible on gastroscopy. In April, 1946, with a recurrence of symptoms and with demonstration of the ulcer again gastroscopically and radiologically at the same site in the stomach as on previous occasions, gastric irradiation (1,600 r) was administered to the body and fundus of the stomach. The radiation produced complete achlorhydria to histamine. The ulcer healed and has remained healed to date, as indicated by absence of symptoms and by repeated roentgen and gastroscopic examinations—the last in 1959. The patient, 86 years of age, continues in satisfactory health.

Comment: This remarkable case again emphasizes the essential role of hydrochloric acid in the pathogenesis and persistence of gastric ulcer. Though the output of acid was small, the elimination of acid by gastric radiation led to complete healing, after 40 years of practically continuously active gastric ulcer—now for 13 years. The absence of gastric carcinoma in a stomach, the site of a persistent gastric ulcer for 40 years, would be in accord with the view that gastric ulcer does not increase the disposition to gastric carcinoma.

CASE 7.—*Fatal Gastric Resection—Acute Heart Failure.*

A 65-year-old housewife, in 1952, had undergone an operation elsewhere for a "stomach ulcer and adhesions." She subsequently experienced several episodes of gastrointestinal bleeding which required blood transfusions. Therapy apparently had consisted chiefly of a proprietary antacid containing aluminum hydroxide. In August, 1953, she was hospitalized because of tarry stools. The history and physical examination indicated the presence of arteriosclerotic cardiovascular disease; the heart was enlarged and the liver was palpable two fingers below the costal margin. Gastroduodenal x-rays demonstrated a large gastric ulcer. Gastric cytology was negative for malignant cells. Therapy with milk and cream and antacids was considered inadequate, though the amount of occult blood in the feces had decreased and the benzidine reaction was negative several days before operation; the hemoglobin on four occasions approximated 11 gm. The patient was not digitalized preoperatively. At operation, she received five units of whole blood and 2,000 cc. saline solution. The patient went into acute congestive heart failure and shock and died within 24 hours despite the use of lanatoside C (Cedilanid) and levarterenol (*l*-norepinephrine [Levophed]) intravenously. The resected stomach contained a depressed scar on the anterior wall of the antrum as well as a benign gastric ulcer close to the pyloric ring. Necropsy demonstrated arteriosclerotic cardiovascular disease with an enlarged liver and spleen.

Comment: Despite the recurrent gastric ulceration and bleeding, the possibility yet remains that more intensive medical management in this case might have controlled the bleeding and obviated hazardous surgery. Indeed, disappearance of occult blood from the feces and maintenance of the hemoglobin suggested that this objective was being accomplished. In any event, the medical management, though perhaps average, was not adequate for this patient. And the gastric resection, though skillfully accomplished, was fatal because of the cardiac problem.

CASE 8.—*Poor Medical Management—Multiple Operations, Multiple Complications.*

A policeman, 38 years old when first seen in June, 1954, nine years previously had been treated elsewhere for a peptic ulcer. Three years earlier he had had an episode of hematemesis and melena. Therapy had been erratic or nonexistent. On June 5, 1954, he experienced severe abdominal pain and three hours later underwent repair of a perforated duodenal ulcer. On June 10, he passed a loose stool. On June 15, he was permitted to return home. On July 22, he was readmitted because of recurrent nausea and vomiting. Gastroduodenal x-rays disclosed an active duodenal ulcer and a very large ulcer on the lesser curvature of the stomach. So far as could be determined from the record, the treatment consisted of milk and cream and small amounts of methscopolamine and phenobarbital for several days; antacids were not prescribed. On August 2, he underwent a subtotal gastrectomy, Billroth I reconstruction, and abdominal vagotomy, with the removal of a large benign ulcer. The postoperative course was stormy. The patient himself had aspirated his stomach in an effort to relieve the severe ulcer pain which was not controlled by the inadequate treatment. The serum electrolytes had not been measured until the day of surgery, with the discovery of a severe biochemical disturbance: Serum chloride, 79 mEq/L; potassium, 3.0 pH, 7.5; serum CO_2, 47.1 mEq/L, and nonprotein nitrogen, 67 mg. %. The electrolyte abnormality was corrected within three days. After a soapsuds enema, the patient developed a prolapse of the rectum and thrombosed hemorrhoids. On the fourth postoperative day, he experienced intractable diarrhea, and on the eighth postoperative day, disruption of the wound. At the time of the third operation, for closure of the wound and a hemorrhoidectomy, the patient was in acidosis with a pH of 7.37 and a serum CO_2 of 6 mEq/L. Three days after this procedure, he developed jaundice, coma, vomiting, and tetany. The urine contained granular and hyaline casts. The patient died on Aug. 2, 1954, despite the usual heroic measures.

Comment: This patient, with recurrent peptic ulceration, did not receive adequate medical management. Gastric resection is not as uneventful as sometimes is suggested.

CASE 9.—*Severe Dumping Syndrome, Malnutrition, after Gastric Resection.*

A 59-year-old man who was first seen in 1951 had experienced ulcer symptoms intermittently for 30 years; a diagnosis of gastric ulcer had been made by x-ray at a Veterans' Hospital during World War I. Symptoms recurred in 1951. In August, 1951, the patient had lost 20 lb. in weight and appeared emaciated. The physical examination also indicated rheumatic heart disease with auricular filbrillation. X-rays disclosed a possible mass on the lesser curvature of the body of the stomach, containing a central ulcer crater 4 cm. in diameter and 1.5 cm. in depth. Several gastroscopies were indecisive. The gastric content contained a maximum of 98 units of hydrochloric acid after histamine. Two additional gastroduodenal x-rays could not exclude a neoplasm. However, gastric cytologic study was negative for malignant cells. A subtotal gastric resection was performed in September, 1951. A huge ulcer on the lesser curvature of the stomach had penetrated into the head of the pancreas. The histologic diagnoses were chronic benign ulcer and atrophic gastritis. Postoperatively, the patient experienced severe dumping syndrome, inability to eat, continued weight loss, and diarrhea. His weight decreased to less than 90 lb. In 1952, several gastroscopies demonstrated severe inflammation in the region of the anastamosis. In 1952 and 1954, hospitalization was required for the management of congestive heart failure. The patient became severely depressed. The dumping problem and the nutritional depletion were unimproved despite the use of dietary and vitamin supplements, sedatives, antispasmodics, and other therapeutic measures. The patient died elsewhere in December, 1954, of a myocardial infarction and congestive heart failure.

Comment: The roentgen emphasis upon the possibility of gastric neoplasm and the indecisiveness of gastroscopy were permitted to outweigh, in diagnostic significance, the 30-year history of recurrent ulcer distress, the substantial amounts of hydrochloric acid in the stomach, and the negative gastric cytology. The gastric resection in this emaciated patient, in retrospect, may have been unwise, because the resultant severe dumping syndrome and serious nutritional depletion proved as incapacitating as the gastric ulcer and probably contributed to the patient's death. An operation was, indeed, justified because of the penetrating ulceration, but a less extensive procedure might have been as effective in dealing with the ulcer and might have been less devastating physiologically.

CASE 10.—*Jejunal Ulcer After Resection of Gastric Ulcer.*

A 46-year-old man, after experiencing heartburn occasionally for many years, passed tarry stools for the first time in October, 1950, and was admitted to a surgical service on Oct. 23, 1950. Gastroduodenal x-rays demonstrated a large ulcer. No other studies were made. On October 24, a subtotal gastric resection was performed with the removal of a benign ulcer. Manifestations of the dumping syndrome developed subsequently. In December, 1952, the patient developed lower abdominal distress after meals and during the night which was relieved by food and alkali. X-rays and gastroscopy demonstrated an ulcer at the gastrojejunal anastomosis. Two measurements of the 12-hour nocturnal gastric secretion indicated no acid and 2.6 mEq. HCl, respectively. Antacid therapy resulted in healing of the ulcer. Symptoms recurred in March, 1953, and x-rays demonstrated recurrent stomal ulceration. The patient underwent an abdominal vagotomy and reconstruction of the gastroenterostomy. In response to a questionnaire in 1956, he reported satisfactory health.

Comment: This patient was not studied or treated adequately during the first hospitalization in 1950. The occurrence of the dumping syndrome after gastric resection is not unusual. The development of a stomal ulcer after subtotal gastrectomy for gastric ulcer is uncommon.

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Evolution of Modern Medicine

This section, which has as its primary purpose a review of the contributions of medical investigators and observers of the past to the present-day concepts of disease, is under the special editorship of Dr. Arthur Bloomfield, 2398 Sacramento St., San Francisco 15.

His editorial in the August, 1957, issue of the A.M.A. ARCHIVES OF INTERNAL MEDICINE, *gives further detail of what it is hoped to accomplish in these articles. Contributions or comments for this section may be sent directly to Dr. Bloomfield, or to the Chief Editor for transmittal to him.*

The Hemolytic Streptococcus Concept in Rheumatic Fever

Clinical Art in Medical Science

ALVIN F. COBURN, M.D., New York

Since the opening sentences of the first preface were written twenty years have elapsed. . . . Of the changes which have taken place in the practice of medicine during these years there is none more striking than the change in the treatment of acute rheumatism. Those who have known that disease under the salicyl treatment can have no idea of the hopeless dread with which one undertook the charge of rheumatic fever in the old days. . . . But all is changed. Rheumatic fever as it formerly existed is unknown to the present generation, and there is now no disease whose treatment the physician undertakes with more cheerful confidence, and which such a certainty of being able to effect a speedy cure. . . . T. J. Maclagan, 1896[1]

Perhaps each generation of physicians points out the current mildness of rheumatic fever in comparison with 20 years ago. In a cyclical disease this occurrence is to be expected, especially since there is available no proper recording of the natural history of rheumatic fever. The student who would learn of the significant points in the evolution of man's knowledge of the rheumatic state must rely on fragments of information as they have appeared in monographs or journals. Furthermore, with the progress of Medicine, the presentation of historical information in medical journals becomes progressively more formal, and the true value of the personal association between clinician and the diseased patient is now dwarfed by the growing importance of scientific data and their statistical significance. At this time, the writer wishes to turn back the hands of the clock momentarily for a retrospective view of a small, but perhaps significant, fraction of the history of rheumatic fever, with particular emphasis on the years 1926 to 1931.

It is well recognized in America that the original ideas on the infectious origin of rheumatic fever and its cyclic nature came from Europe in the late 19th and early 20th centuries.[2-5] These concepts were the product of *observations* by clinicians. The conclusions reached were particularly valuable when drawn from epidemics of rheumatic disease, especially when preceded by tonsillitis as described in 1886 by Haig-Brown.[2] Now, however, one notes an increasing lack of appreciation for the worth of careful clinical observation. It appears that accurate data must come from machines! In fact, the opportunity for a student to do a piece of original work may well seem to him surrounded by a high wall of forbidding reali-

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ties; for example, the requirement of a well-designed laboratory, multiple research grants-in-aid, the latest in electronic equipment which will relieve the human mind of making computations, and finally, a team of workers to share responsibility. Moreover, it may appear that the proposed research will require the approval of committees, intercontinental cooperation, and perhaps even the involvement of "Parkinson's Law".[6] The student is not told that this wall of practicalities is only a man-made artifice and that Nature still gives away Her secrets, selectively, to the inquiring mind. Nevertheless, it is still true that the hospital resident of tomorrow, engaged in uncommitted research, may single-handedly guide others to the solution of an important disease problem, and perhaps his lead will stem from the accuracy of a clinical observation which others failed to make.

To point out one example of a hospital intern's investigations, I am recording my personal association with the factor of infection in the rheumatic state that occurred while I served as a member of the house staff of the Presbyterian Hospital of New York, from 1925 to 1931. In suggesting that mind and bedside rapport may, on occasions, be more useful than gadgets and statistics in medical research, I will commit the unforgiveable error of exposing immodestly my close, deep, human contact with a disease whose prevention appeared impossible in 1926. Moreover, I must confess in advance that I began my research without either a working hypothesis, an experimental design, scientific training, or even a laboratory bench of my own. I had only a challenging but undefined problem, a few sick children, and an invaluable association with a rare, creative thinker, Dr. A. R. Dochez. In the instance to be reported, the inspiration emanating from Dochez and a close rapport with patients more than compensated for the lack of tangible aids.

At the beginning it must be emphasized that the basis for my work was already prepared by preceding generations of clinicians. In his classic of 1889, Cheadle indicated that tonsillitis must be included among the various manifestations of the rheumatic state.[7] The importance of the preceding throat infection was frequently restated by other English physicians. Moreover, the epidemiologist, Glover, desc. ibed an outbreak of 41 cases of rheumatic fever after an epidemic of 427 cases of tonsillitis in 1930.[8] However, bacteriological studies of these infections had not been made. Later in the year, Schlesinger reemphasized the relations between pharyngitis and rheumatic fever in children. The throat flora of these patients with pharyngitis preceding rheumatic fever was studied. However, hemolytic streptococcus did *not* appear significant.[9] In 1930, the consensus among those who believed in the bacterial hypothesis was that one or more classes of nonhemolytic streptococcus were implicated in rheumatic fever, as had already proved to be the case in subacute bacterial endocarditis. At the end of 1930, on December 24th to be exact, I distributed "The Factor of Infection in The Rheumatic State" in which the hemolytic streptococcus concept was presented.[10] Confirmation that a hemolytic streptococcus was associated with activation of the rheumatic process was soon forthcoming from the English investigators, Collis,[11] Sheldon,[12] Griffith,[13] Glover,[14] and Bradley.[15] It is significant that, with the exception of perhaps Griffith, all of these men had close associations with rheumatic fever patients and their preceding infections.

However, it was not until more than a quarter century had elapsed that I became conscious of the true value of this simple patient-physician rapport. On Jan. 3, 1959, my second rheumatic fever patient (ref. 10, p. 137) reappeared.

In December of 1926, the patient had resembled the picture on the frontispiece of Cheadle's classic[7] when admitted to Medical Ward 11 of the old Presbyterian Hospital in New York. He appeared a pale, thin boy of twelve, critically ill with rheumatic pancarditis characterized by intense precordial pain.

The consensus was that this boy could not recover. However, he unexpectedly survived this

intense rheumatic attack but remained chronically ill until January, 1929. At that time, I transported him, among a group of children, to Puerto Rico, where he became free of rheumatic activity.* Subsequently, he escaped hemolytic streptococcal infection and, in spite of aortic and mitral valvular lesions and an enormous heart, he remained well compensated. For several years, he worked with restricted activities in medical research; later, he became the father of four children; now he is a "detail man" for a pharmaceutical company and without any physical limitation.

In January, 1959, this patient recalled to me the death of another patient, a little Italian boy with rheumatic fever, on the opposite side of Ward 11 (ref. 16, p. 583).

This boy had had an enlarged rheumatic heart with aortic and mitral valvular lesions when admitted in the Fall of 1926 with Type 2 pneumococcus lobar pneumonia. There occurred a spread to a second and a third lobe, and the patient became unconscious. In addition, he developed cervical adenitis, which subsequently formed a staphylococcus abscess. Moreover, as a result of an indwelling catheter, he developed cystitis and a bloodstream infection with colon bacillus. Nevertheless, throughout those critical weeks, the boy's heart remained compensated, and he walked out of the Presbyterian Hospital some months later. It seemed extraordinary that, with an overwhelming pneumococcus infection and severe complications, there had been no signs of heart failure.

When, early in 1927, this boy developed a "sore throat," his Italian-born family would let no other doctor see him except, as they believed, "the man who had saved his life!" As his medical intern, I was summoned to the Presbyterian Hospital accident ward on Park Avenue at 70th Street, where I found he had acute pharyngitis. The illness was mild and I sent him home to gargle and remain in bed. A throat culture showed that there was hemolytic streptococcus in his throat flora, which at that time seemed of no significance. However, the patient returned a week later with symptoms of rheumatic fever and was readmitted to Ward 11. There he soon developed a fulminating rheumatic attack with rapidly progressive cardiac insufficiency followed by death.[16]

This was a humbling experience. I had sent this boy home with what appeared to be trivial pharyngitis. Why had his heart, which had acted extraordinarily well during three severe bacterial infections, failed so rapidly when he developed an attack of rheumatic fever? Why was this mild pharyngitis followed by a fulminating rheumatic attack when there had been no rheumatic recurrence after the dangerous bacterial diseases which had occurred during his previous hospital admission? It was this humiliation, this ignorance, this curiosity, but especially this strong rapport between a medical intern (who had obviously failed) and a rheumatic boy (who had manifested faith in his ward doctor) that forced me into rheumatic fever research. And there was to be answered the question, "What caused that pharyngitis which precipitated the boy's fatal illness?" Could it possibly be the ubiquitous agent, hemolytic streptococcus? To answer this question there was available only a throat swab, a Petri dish containing blood-agar, and the customary (as of 1927) close human relationship between a medical intern and his patient.

The following years of 1928 and 1929 proved to be the critical ones in evaluating the possible role of hemolytic streptococcus as a significant agent in the genesis of rheumatic fever. After the autopsy on this patient,[16] there occurred at the Presbyterian Hospital three significant developments in the evolution of the hemolytic streptococcus concept.[10] Each resulted from a close physician-patient relationship.

The first was the throat culture observations accumulated among rheumatic children living in several boroughs of New York; which, in late 1928, resulted in the hypothesis that hemolytic streptococcus may be the agent which precipitates rheumatic fever. The second was the transplantation experiment, beginning on Jan. 11, 1929, in which children with chronic, persistent rheumatic fever and with hemolytic streptococcus in the throat flora were transported to Puerto Rico. The third, the application of antibacterial prophylaxis in rheumatic children, was initiated in New York during April, 1936,

* This study was made in 1929 when the island, now Puerto Rico, could be reached only after a long sea voyage and when scarlet fever and rheumatic fever rarely occurred in San Juan. Coincident with or subsequent to the development of rapid air transportation, changes have occurred in the geographical distribution of many infectious processes.

and reported in January, 1939.[17] A similar study, initiated and reported concurrently and independently by Thomas and France [18] from The Johns Hopkins Hospital, proved to be invaluable. To many persons, the observations on the Baltimore rheumatic patients were convincing. Nevertheless, it was the Puerto Rican transplantation experiment which influenced some of my close associates and made possible the publication of my original work.[10] These (1927-31) developments on the significance of hemolytic streptococcus, made possible by rheumatic patients, are summarized in the Table.

Distribution of "The Factor of Infection in the Rheumatic State" on Dec. 24, 1930, was made to 50 interested persons. The acknowledgments by recipients varied strikingly. Some showed no positive reaction. For example, Dr. John R. Paul, who kindly wrote a generous letter of thanks and congratulations on Jan. 13, 1931, did not discuss hemolytic streptococcus. This was also the case in his excellent monograph on "The Epidemiology of Rheumatic Fever," 1930,† in which he included a note on "The Factor of Infection in the Rheumatic State." Moreover, the name hemolytic streptococcus did not appear in Dr. Paul's description of the bacteriology of rheumatic fever in the 1932 edition of "Piersol's Cyclopedia of Medicine." On the other hand, the majority of recipients did manifest positive responses to the hemolytic streptococcus concept. These fell mainly into three distinct types.

Chronology of Developments in the Hemolytic Streptococcus Concept in Rheumatic Fever (1922-1931)

Date	Investigator	Observation
Jan., 1927	Coburn, A.	Fulminating rheumatic fever after hemolytic streptococcus pharyngitis, Presbyterian Hospital, created a problem.
Jan.-July, 1929 *	Coburn, A.	Puerto Rican experiment indicated a possible significance between hemolytic streptococcus and rheumatic activity.
March, 1930	Glover, J.	Milroy lectures re-emphasized the important relation of epidemic tonsillitis to rheumatic fever.
Dec. 24, 1930 †	Coburn, A.	Distributed "The Factor of Infection In The Rheumatic State" to interested persons.
June, 1931	Sheldon, W.	Publication-clinical observations confirming importance of throat infections in rheumatic fever.
June, 1931	Collis, W.	First bacteriological report confirming hemolytic streptococcus concept in rheumatic fever.
Late 1931	Griffith, F.	Annual Report of Chief Medical Officer of the Ministry of Health for 1930, commending the hemolytic streptococcal concept.‡
Sept., 1931	Glover, J. & Griffith, F.	Substantial bacteriological confirmation of hemolytic streptococcal concept.
Sept., 1931 (Submitted)§	Bradley, W.	Convincing epidemiologic confirmation of hemolytic streptococcal concept.

* See the review on "The Rheumatic State" by J. H. B. in Bulletin of American Heart Association, Vol. 6, No. 2, March, 1931.

† Date was changed to Jan., 1931, by the publishers when this paper-covered monograph was bound.

‡ Published in 1931.

§ Published Jan., 1932.

First, there was the friendly reaction of "The Agnostics." No American had worked more earnestly on the rheumatic fever problem than the well-recognized microbiologist, Dr. Homer F. Swift. Although open-minded and interested in my monograph, as shown in his letter of Jan. 2, 1931, Dr. Swift was skeptical. For some years he did not know whether hemolytic streptococcus initiated rheumatic fever, and as late as 1939, he published on filterable agents in rheumatic fever exudates.[19]

THE HOSPITAL OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH
66th Street and York Avenue, New York
January 2, 1931

Dr. Alvin F. Coburn,
Presbyterian Hospital,
168th Street and Broadway,
New York.

Dear Doctor Coburn:

Thank you so much for the copy of your book, The Factor of Infection in the Rheumatic State. I have anticipated seeing this book for some time and of course am delighted to have one autographed by the author. Naturally I have not yet been able to read it completely but have gone through it enough to realize that you have called attention to many important factors in the disease. I am particularly interested in your point of view concerning hemolytic streptococci, for we have felt for some time that they have more to

† The exact date of publication as given to The New York Academy of Medicine by The Metropolitan Life Insurance Company was July 28, 1931.

THE JOHNS HOPKINS UNIVERSITY

DEPARTMENT OF PATHOLOGY

1833 EAST MONUMENT STREET
BALTIMORE, MARYLAND

Dr Alvan F Coburn
New York

Dear Dr Coburn

Please accept my best thanks for the copy of your book on the Rheumatic State. I have gone over it already with great interest - and gather that you feel that this is a peculiar vaccine associated with upper respiratory infection with the haemolytic Streptococcus - Very well - but the lesions are so absolutely specific that I am still betting on a perfectly unique infection agent. And am glad you did not find the Streptococcus in the blood in 99%

Sincerely yours

W G MacCallum

Jan 9
31

do with the disease than most people think probable. For this reason we have investigated the action of vaccines prepared from hemolytic streptococci, and, as you may have heard, have had very satisfactory results.

I wish you every success in your future work in this subject which is of so much interest to all of us.

With the season's greetings,

I remain,

Yours sincerely,
Homer F. Swift

Second, the point of view of "The Loyal Opposition" was succinctly expressed by the writer's own distinguished and esteemed teacher, his Johns Hopkins Professor of Pathology, Dr. William G. MacCallum. In his letter of Jan. 9, 1931, Dr. MacCallum wrote: "You feel that this is a peculiar reaction associated with upper respiratory infection with the hemolytic streptococcus—Very well—but the lesions are so absolutely specific that I am still betting on a perfectly unique infectious agent."

Third, there was a small minority which not only soon accepted the hemolytic streptococcus concept but also contributed much to its furtherance. This was the group of "Enthusiasts." Whereas it was the pathologist that led "The Loyal Opposition" and the microbiologist that pointed the way for "The Agnostics," it was the young English clinician, Collis, who in his letter ‡ of Jan. 29, 1931, supported wholeheartedly the hemolytic streptococcus concept and later formed a nucleus for "The Enthusiasts." [11]

THE HOSPITAL FOR SICK CHILDREN
GREAT ORMOND STREET
LONDON, W.C.I.

29th January, 1931

Dear Coburn,

Thank you very much for your fascinating book which I have read with the greatest interest. I think it is quite the most interesting work on rheumatic fever which has appeared. I am glad to say that we are able to confirm your attitude, indeed at the moment I am writing a paper on the epidemiology of rheumatic fever which almost exactly coincides with your view of the haemolytic streptococcus, and brings in not only more than one epidemic of rheumatic fever in rheumatic homes caused by the haemolytic streptococcus, but also reports epidemics of primary rheumatism associated with haemolytic streptococcal sore throats. I am sending you the first reprint I get of this paper, which I am sure will interest you. I cannot at the moment give you more details and I hope you will keep what I have said confidential.

It was curious that although we met during the summer we didn't discuss the haemolytic streptococcus. At that time, however, I was very uncertain of the ground we stood on and it has only been during this winter that we have been able to completely convince ourselves. Your book has caused great rejoicing in that it has confirmed our views, or perhaps better our work will confirm yours.

I was over in Ireland at Christmas and all Dermot's family were in very good form and were continually asking after their American relations.

Best wishes to you and all my friends at the Presbyterian Hospital and the wolf hounds,

Yours aye,
Bob Collis

This glance back at the reaction of 1931 should hearten the beginner in medical research. Although Dr. MacCallum was America's most esteemed pathologist, he saw rheumatic fever only post mortem. His concepts came from what he saw on examining tissues in the microscope. Likewise, whereas Dr. Swift was America's most qualified investigator of rheumatic fever, he saw the disease only after an attack had been initiated. Dr. MacCallum dealt with ashes, and Dr. Swift handled fire. But it was Collis, Sheldon, Glover, Bradley, and other English investigators who dealt with the throat infections which preceded rheumatic fever. In retrospect, it seems natural that it was the simple power of observation of young clinicians, who had a close rapport with patients, that detected the spark which initiates activity of the rheumatic process. Likewise, one can reasonably expect that untrained men of the future will make the

‡ When Collis wrote in his second paragraph "we met during the summer" he must have had in mind Dr. Yale Kneeland Jr., also of New York's Presbyterian Hospital. Coburn remained in New York; however, Kneeland did visit Collis in London in the summer of 1930. At that time, during a conference with Collis and F. Griffith, Kneeland told Collis that Coburn's findings associating hemolytic streptococcus with rheumatic fever were in press and would be available to him soon.

significant discoveries in areas which their teachers may have overlooked.

Comment

The purpose of this communication is to emphasize the continuing significance of the patient-physician rapport in one small fraction of the evolutionary development of rheumatic fever research. Perhaps the best example of this significance was that of Dr. Kingston J. Fowler, who was both patient and physician! In 1874, Dr. Fowler had a severe attack of rheumatic fever. He was cared for by Dr. Garrod, who inquired of Fowler whether he had experienced a sore throat preceding his attack of acute rheumatism. A train of thought was initiated in the *patient!* This resulted in the *physician,* Fowler's report in the Lancet of Dec. 11, 1880, on the "Association of Affections of the Throat With Acute Rheumatism." [20] During those years of 1874-80, both Dr. Garrod and Dr. Fowler observed that at least 80% of acute attacks of rheumatic fever were initiated by pharyngitis. This accurate observation, made in the 19th century, has proved to be the useful base for 20th century studies.

However, in the decade 1930-40, "The Loyal Opposition" and "The Agnostics" were overwhelming in numbers, and the hemolytic streptococcal work would have been terminated had it not been for unsolicited help from abler research workers in other countries. By pure happenstance, the writer's studies and his publication of the hemolytic streptococcus hypothesis preceded the bacteriological reports of British colleagues. However, it was not long before I became more deeply indebted to European scientists than I can explain herewith. First, it was published confirmations by "The Enthusiasts" in England that made possible the continuation of the hemolytic streptococcal studies in New York in 1932-38. Moreover, it was the generous and invaluable help from the laboratories of Dr. Edgar Todd [21] and Dr. Fred Griffith [22] that made possible, in 1933-39, the support of the writer's research in his pursuit of a method for the prevention of rheumatic recurrences.[23-25] Later, it was the selfless devotion of Dr. Rebecca Lancefield to the chemistry of hemolytic streptococcus that stimulated the interest of others. Finally, it was the epic discovery of Domagk [28] that provided antibacterial prophylaxis. This, as indicated by Thomas in her Bruce Memorial Lecture,[29] facilitated acceptance of the concept that hemolytic streptococcus is the factor of infection in rheumatic fever.

In concluding I would like to re-emphasize certain convictions that I have reached after more than 30 years' association with rheumatic fever research. The student or the unqualified house officer has great opportunity to contribute to medical knowledge. In fact, his findings may transcend those of his well-trained and more experienced seniors working in the laboratory with preconceived ideas. Certain laws are irrevocable and eternal. For example, Nature tells Her secrets to the inquiring mind irrespective of age, sex, training, color, creed, geographical location, or any man-made barriers. The nub of all clinical investigations remains a close rapport between physician and patient. Irrespective of the precision of a measurement or the enormous cost of an instrument, there is no substitute for the human intellect and its power to make accurate observations.§ Most disease problems today are attacked by a team of collaborators. Some of the team will understand (in part at least) their instruments of precision; others will understand the intricacies of biostatistics, be able to determine the P value and inform all

§ The keen observer, Christopher Columbus, trained in the *art* of navigation, performed in 1492 a creative function for which all Americans are indebted. In striking contrast, the pilot of a modern Lockheed Electra airplane, trained in the *science* of navigation and aided by millions of dollars of electronic instruments of precision, failed in 1959 to steer his ship to the designated runway. Within minutes prior to this tragedy, another pilot operating a small plane had no difficulty in making a routine landing on this runway. This pilot, in the absence of radar, used his powers of observation; whereas reliance on machine-made altitude determinations produced death and destruction of the Electra.

members whether the results are positive, negative, or equivocal. The team attack is a tremendous advance of the 20th century.

Nevertheless, to investigate disease problems on the patient level, the original mind needs the clinical milieu in which, alone, he may do uncommitted research. This opportunity the seeker must forge for himself. It is essential for the creative mind to escape the man-made devices of a "formalized project," planned realistically by an experienced committee. Likewise, he must free himself of concern for speed of production and always hold faith with the truth that the matter of priority may prove a "competitive inhibitor" and, at best, is of only historical interest.‖ On the other hand, he must sense that, through the quality of any man's imaginative effort, there may come a unique discovery.

In many ages and places, the original discoveries of creative physicians have been of incalculable value. For me the bedside observations of 19th- and 20th-century British physicians formed a solid base. Moreover, when most needed, help came unsolicited (as it always does to the patient investigator) from understanding laboratory workers who lacked the bedside association. Their generous gifts were made at critical points in the defense of my concept. One can assure today's beginner in clinical investigation that he too will receive his greatest help from minds of the modest, retiring, original, creative, but *not* gregarious, colleague in the laboratory. Clinical art is continuously nurtured by medical science. Hence, it is to the Edgar Todds, to the Fred Griffiths, to the Rebecca Lancefields, and to the other creative scientists of their stature, who made possible the evolution of a concept from the theory stage of an untrained hospital intern to a practical plan of action for the prevention of rheumatic fever, that I wish to record a debt that can no longer be paid and to express an appreciation whose "half-life" is Infinity.

14 Ludlow Drive, Chappaqua, N.Y.

‖ Even well-documented, original work may be lost. For example, I have only recently discovered with delight that in 1906 Major Charles F. Kieffer of the United States Army not only described the relation between tonsillitis and 276 cases of acute articular rheumatism but also pointed out that the "incubation period varied between three and thirty days with an average of 24 days." Furthermore, he did a study in prophylaxis with 120 of his cases of tonsillitis at Fort D. A. Russell in Wyoming. Half of Kieffer's "parallel series" received the commonly used throat mixtures. The other half received acetylsalicylic acid. Of the sixty controls, "nine of the patients subsequently developed acute articular rheumatism." Of the 60 treated with acetylsalicylic acid, Kieffer wrote in 1906, "Finally, *in this series not one case of rheumatism developed.*"[28]

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Contributions of Basic Science to Modern Medicine

Restrictions Imposed on Antibiotic Therapy by Renal Failure

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When a drug which is normally excreted in large part by the kidneys is administered repeatedly to a patient with renal failure, it will tend to be retained and may accumulate in the body. The retention of large amounts of certain drugs can produce undesirable effects so that it may be prudent to reduce the size or frequency of the doses. On the other hand, undue caution may deny the patient adequate therapy and be as disadvantageous as overzealous treatment.

Prolonged administration of large doses of some of the antibiotics currently in clinical use is not entirely innocuous. Liver and renal damage, negative nitrogen balance, and increased excretion of riboflavin as well as certain vitamins and amino acids into the urine may occur in patients treated with any of the tetracyclines.[1-9] Renal damage has been noted with the use of bacitracin,[10-14] the polymyxins,[15-22] neomycin,[15,23] and kanamycin.[24] Damage to vestibular or auditory function occurs with streptomycin and dihydrostreptomycin,[25] neomycin,[15,23] kanamycin,[24] and vancomycin;[26,27] bone marrow depression[28] and the so-called "gray syndrome" (cardiovascular collapse) in infants[29] has occurred in association with chloramphenicol therapy. It is therefore important to use these drugs in such a manner that maximum therapeutic advantage is obtained with a minimum of toxic hazard. This is particularly important in the uremic patient for whom ordinary therapeutic doses may actually be excessive and in whom drug toxicity may threaten life.

The antibiotics lend themselves fairly well to the analysis of the problem of dosage in patients with renal failure because (1) many of them depend largely on the kidneys for excretion, (2) microbiologic assay of antibiotic content of serum and urine have direct therapeutic significance, and (3) single test doses may be given to uremic patients with reasonable safety.

Control of the Concentration of Antibiotics in the Blood

With few exceptions, most pharmacologic studies of antibiotics in man have not been designed to provide data which could be used to predict or control the concentrations of drug in the blood of patients with renal disease. This is not surprising in view of the crude microbial methods of assay commonly used and the fact that dosages are usually designed to give an excess of drug over that which is necessary for therapeutic efficacy.

Boxer et al.[30,31] studied the kinetics of the removal of streptomycin from the blood of dogs and man after single and multiple injections. They derived formulas which govern the size and frequency of the dose needed to produce a constant concentration of drug at any desired level. To apply these formulas it is necessary to know the ap-

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parent volume of distribution and the elimination rate constant of each specific drug. Since the rate of fall in the blood levels for all antibiotics studied is proportional to their concentration, the concentration (C) at any given time (t) will be

$$\text{(I)}\quad \log C = Kt \cdot \log Co$$

or,

$$\text{(II)}\quad C = Co \cdot e^{Kt}$$

where K is the elimination rate constant and Co is the extrapolated maximum concentration at time zero.* Co is derived experimentally from the analysis of a single dose curve and may be to calculate the apparent volume distribution (Vc) by the formula:

$$\text{(III)}\quad Vc = \frac{\text{amount of drug injected}}{Co}$$

Conversely, the value of Vc can then be used to determine Co for any given dose.

Since elimination rates are exponential, the concentration of any antibiotic which is given repeatedly will approach an upper limit, after which an essentially steady state will be reached. The concentration at any point in time after such a steady state has been achieved can then be calculated from further equations presented by Boxer et al.[30,31]

These concepts are important because (1) drugs with rapid elimination constants will tend to reach a steady state at high concentrations only when large doses are given frequently, (2) conversely, drugs with slow elimination constants will tend to reach a steady state at high concentrations even when given in relatively small doses or infrequently, and (3) factors (such as renal disease) which tend to decrease the elimination rate of drugs dependent upon the kidneys for excretion likewise lead to high concentrations of drug, even when small doses are given infrequently.

In the last two instances, however, an essentially steady state would be reached rapidly during high-dose therapy, so that for practical purposes the magnitude of the concentration in the blood, even under these circumstances, is limited.

Kunin, Dornbush, and Finland[32] studied the kinetics of the clearance of the tetracyclines from the blood and presented formulas which are useful in analyzing the contributions of renal and nonrenal mechanisms to the elimination of these drugs from the body.

Boxer et al.[30,31] also used the half-life of a drug in blood as a convenient expression of its persistence. The relation between half-life (T/2) and elimination rate constant is

$$\text{(IV)}\quad T/2 = \frac{0.693}{K}$$

The extent to which the elimination constant or half-life will be affected by the presence of renal disease depends primarily on (1) the rate at which the drug is cleared by renal mechanisms, (2) the rate at which the drug is cleared or destroyed by nonrenal mechanisms, and (3) the severity of renal impairment.

An analysis of the manner in which the half-life of an antibiotic in serum may vary with changes in renal function is presented in Figure 1. Two hypothetical drugs are considered. Drug *A* is stable and cleared only by renal mechanisms; its serum

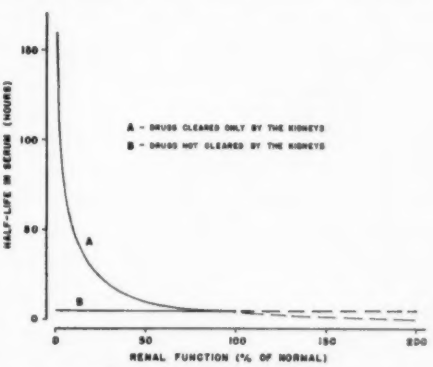

Fig. 1.—Hypothetical representation of relation between half-life of an antibiotic in serum and the degree of impairment of renal function for two classes of antibiotics, one cleared only by the kidneys and the other cleared only by nonrenal mechanisms. Reproduced with permission from the editors of the *Journal of Clinical Investigation* 68:1517 (Sept.) 1959.

* Some of the symbols employed in the formulas presented in this paper may vary from those employed in standard texts and in the papers cited; this was done in order to keep them consistent here.

half-life is theoretically determined only after distribution and equilibration in body compartments has occurred; its clearance is independent of the rate of urine flow, and its relative distribution volume is independent of the integrity of renal function. Drug *B* is removed from the blood entirely by nonrenal mechanisms.

The curve described by drug *A* is derived from an analysis of such a substance, mannitol, by Newman et al.[33]; they found that the relation between the clearance of mannitol by the kidneys and the fall in its levels in plasma after a single intravenous injection could be expressed by the formula

$$(V) \quad Cl_r = Vc \cdot K$$

where Cl_r is the rate of renal clearance (in Figure 1, expressed as the per cent of normal function including all modes of renal excretion), Vc is the apparent volume distribution of the substance, and K is the elimination rate constant. Thus, according to this formulation, the serum elimination constant will vary directly with changes in renal function and, therefore, the half-life in serum will vary inversely with changes in renal function. It is apparent from Figure 1 that the most marked change in serum half-life (an abrupt prolongation) begins to occur at a point at which renal function has fallen below 25% of normal or at the point at which one expects the urea nitrogen, creatinine, or uric acid in the blood to rise.

The serum half-life of drug *B* is entirely independent of the degree of renal function.

Actually, very few drugs, and certainly none of the antibiotics in current use, meet all of the specifications for either Drug *A* or Drug *B*, although some come very close to doing so (*vide infra*). Furthermore, the apparent volume of distribution cannot be expected to remain constant while renal function varies from normal to that of advanced uremia (in part, because of fluid retention that may occur in uremic patients). Finally, a substantial amount of each of the antibiotics is removed by nonrenal mechanisms which, in turn, may be affected by the presence of renal disease.

Thus, curves relating changes in renal function to the rate of decrease of antibiotics in blood must be constructed empirically. Examples of such curves are presented in Figures 2 and 3. The data used to construct these curves were obtained by selection of a series of patients with varying degrees of renal impairment, as estimated by the 24-hour endogenous creatinine clearance.[34,35] Each patient was given a

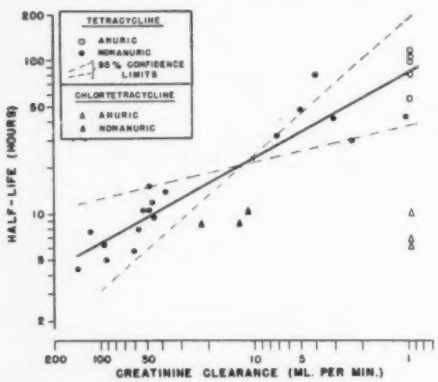

Fig. 2.—Relation of half-life of tetracycline in serum to creatinine clearance following an intravenous dose. Some observations on the half-life of chlortetracycline in three anuric patients and in three patients with normal renal function are also included for comparison. Reproduced with permission from the editors of the *Journal of Clinical Investigation* 68:1490 (Sept.) 1959.

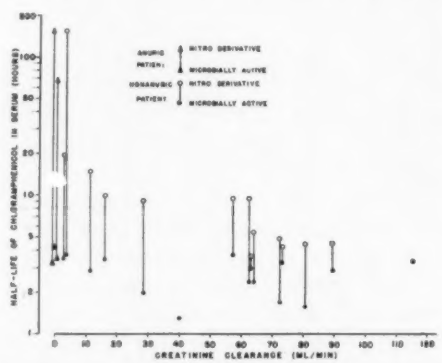

Fig. 3.—Serum half-life of microbially active chloramphenicol and of total nitro compounds following an intravenous dose of chloramphenicol as related to creatinine clearance. Reproduced with permission from the editors of the *Journal of Clinical Investigation* 68:1502 (Sept.) 1959.

single intravenous injection of the antibiotic under test, and the half-life in serum was calculated from the slope of the serum decay curve.

Figure 2 also demonstrates the marked difference in behavior of the two analogues, tetracycline and chlortetracycline; the former resembles the theoretical curve *A*, while the latter resembles *B*. It is to be noted, however, that in the case of tetracycline (despite the similarity to curve *A*) the anuric patients did not retain the drug so long that the half-life was much in excess of 100 hours whereas, theoretically, the drug should have been retained indefinitely.

Figure 3, which depicts the results obtained with chloramphenicol, demonstrates the same type of relationship between drugs; in this instance, between microbially active chloramphenicol and its metabolic products. Whereas the half-life in serum of the active drug is virtually unchanged, regardless of the severity of renal disease, the metabolic products are retained in much the same manner as Drug *A* or tetracycline.

Control of the Concentration of Antibiotics in the Urine

The concentration of an antibiotic excreted into the urine at any point in time depends upon the concentration in the blood, the rate at which it is cleared by the kidneys,[36] the rate of urine flow, and the functional capacity of the kidneys. Sirota and Saltzman,[37] in a study of the renal clearance of chlortetracycline (Aureomycin) in man, showed that the ratio of urine/plasma concentration of the antibiotic could be predicted by simple calculation from the formula

$$(VI) \quad \frac{Ua}{Pa} = \frac{0.35F}{V}$$

where Ua/Pa is the ratio of urine to plasma concentration, V=rate of urine flow in mililiters per minute, F is the glomerular filtration rate in mililiters per minute, and 0.35 is the ratio of the clearance of the antibiotic to that of creatinine, Cl_a/Cl_{creat}.

Formula VI was adapted for construction of the theoretical curves presented in Figure 4. Three hypothetical antibiotics are considered in this figure; each is identical in all respects except for the ratio of their rates of renal clearance to that of creatinine. One drug is cleared at a rate equal to that of creatinine (100%), a second is cleared half as well (50%), and the third, one-quarter as well (25%). The rate of urine flow is constant at 1 ml/min. The horizontal broken line roughly delineates the minimum effective concentration ratio of drug in the urine, and the vertical broken line marks the level of creatinine clearance below which azotemia begins to appear.

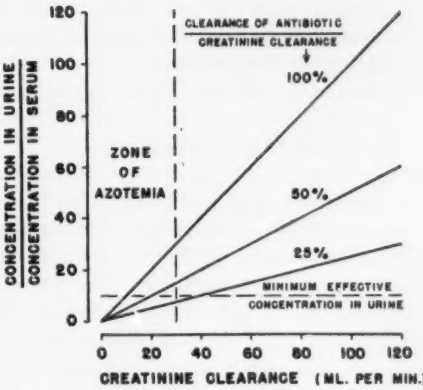

Fig. 4.—Relation between urine/serum concentration ratios and creatinine clearance for three hypothetical antibiotics which have renal clearances that are 100 per cent, 50 per cent and 25 per cent, respectively, of the creatinine clearance.

This figure would indicate that when the concentration of an antibiotic in the blood and the rate of urine flow are constant, its concentration in the urine will be directly proportional to its renal clearance and to the renal functional capacity. Thus, for the treatment of infections of the urinary tract, high concentrations of drug in the urine will be more readily achieved by rapidly excreted antibiotics. These considerations may enter into the choice of drug, as, for example, the most favorable tetracycline analogue for the treatment of urinary tract infections (*vide infra*).

Certain physical and chemical characteristics of each drug also determine whether or not an antibiotic will be retained in the

presence of renal failure. Some of these properties are (1) inherent stability, (2) mode and extent of renal removal, (3) other modes of excretion (through conjugation, excretion into the bile and gastrointestinal tract), (4) plasma protein binding, and (5) sequestration and release from various organs such as the liver.

Some of the antibiotics in common use will now be considered in the light of available data concerning their potential for accumulating in the body, the properties of the drugs which may lead to their retention, and the alternate nonrenal pathways for their removal from the body. Part of these data have been drawn from studies performed in this laboratory on renal clearance of antibiotics and the persistence of antibiotics in the blood of patients with acute renal failure.[32,34,35]

Penicillin

Penicillin, a remarkably nontoxic drug, has been given in huge doses to man with notably few ill effects.[38] Despite in vitro data, indicating that as much as 48% to 58% is bound to plasma proteins (mostly to albumin),[39-41] it is cleared by the kidneys at rates variously reported as 560-1080 ml/min.[42,43] Rantz et al.[43] found that the renal clearance of penicillin may increase 50% in the presence of fever, presumably owing to increases in the renal blood flow. Not all of a parenterally administered dose of penicillin can be recovered in the urine, despite its rapid renal clearance. Rammelkamp and Keefer[44] recovered only 58% of an intravenous dose; Tompsett et al.[45] reported an 85% recovery following intramuscular injection. Rowlands et al.,[46] using penicillin labeled with radioactive sulfur in cats, recovered only about 36% to 66% of the administered dose in the urine.

Penicillin G is slowly inactivated in aqueous solutions; at pH 7.5, its half-life is 60 hours.[47] Eagle found that penicillin G added to human serum, when incubated at 37C, is inactivated at a rate of about 10% per hour, corresponding to a half-life of about seven hours.[48]

The liver may play an important role in the inactivation of penicillin in vivo. Anderson and Broderson[49] demonstrated that the clearance of penicillin from the plasma of dogs was markedly decreased following bilateral nephrectomy, and it was further reduced by the performance of hepatectomy or evisceration together with bilateral nephrectomy. Kunin and Finland[50] noted that, in man, the half-life of penicillin G was more prolonged in patients with both severe liver disease and anuria than in patients suffering from anuria alone.

In patients without renal disease, the half-life of aqueous penicillin G following a single intravenous dose, as calculated from the data available in the literature,[51] is about one-half hour, and following an intramuscular injection, about one hour. Presumably, even a shorter half-life may be expected in febrile patients in whom the renal blood flow and, consequently, the renal extraction of penicillin are enhanced.[43]

A number of investigators have pointed out that the removal of penicillin from the blood is reduced in the presence of renal failure[50,52-56] in premature infants and in aged persons, whose renal function is also below normal. In 1944, Humphrey[52] reported observations on two anuric women who had been given a single injection of aqueous penicillin G; he was unable to recover the drug in the small amount of urine excreted but demonstrated diminishing penicillin activity in the serum for up to five days in each patient. Similar observations have been reported by Jensen et al.[55]

In an attempt to quantitate the persistence of penicillin in the blood of patients with anuria and severe renal failure, we[50] have observed that the half-life of aqueous penicillin did not exceed 10 hours unless severe hepatic disease was also present. Thus, even when the renal contribution to the removal of penicillin from the body was negligible, the drug was nevertheless removed from the blood at a rate of 7% to 10% per hour. Bull[57] suggested that a single injection of penicillin be given daily to an

anuric patient. Also, a large accumulation of active penicillin cannot be expected to occur in anuric patients on continuous therapy because of the fairly rapid removal rate and the factors governing accumulation, as outlined by Boxer et al.[30,31] (*vide supra*).

To maintain therapeutic levels of penicillin in patients with renal disease following a loading dose, intermittent injections of aqueous penicillin must be given at intervals of 4 to 12 hours, depending on the severity of renal impairment and the dose of penicillin ordinarily required to cure a particular infection. Probenecid and repository forms of penicillin also have much less of a place to augment or prolong penicillin levels in uremic patients.

Streptomycin

Undesirable complications of streptomycin therapy (aside from allergic phenomena) are bilateral damage to the vestibular function; less frequently, nerve deafness, and rarely, agranulocytosis.[25,58-65] The occasional nephrotoxicity reported as first[66] was probably due to peculiarities of certain lots of streptomycin and has not been a problem in recent years. Dihydrostreptomycin toxicity is most frequently manifested as nerve deafness, but vestibular damage may also occur. The combined use of the two analogues has been reported to result in a decrease in the incidence of vestibular complications, but this advantage is offset by a greater incidence of hearing loss than is noted when streptomycin is used alone.[64]

The toxicity associated with these drugs appears to be related to the magnitude and the duration of therapy.[25,58-65] Toxic manifestations commonly occur in patients with renal disease[58,65,67] even after relatively short courses of therapy, presumably owing to rapid accumulation of the drug in these cases.

Streptomycin is very stable under ordinary conditions in vitro.[68] Boxer et al.[30] reported the serum half-life after intramuscular injection in normal subjects to be 2.72±0.47 hours; Kunin and Finland[50] reported a value of 2.4 hours for normal subjects, and similar values may be obtained by recalculating the data reported by others.[25]

Several investigators, employing various techniques of assay, have reported that streptomycin is cleared in the kidney by glomerular filtration at rates varying from 30-70 ml/min.[31,69,70] Boxer et al.[31] found that the rate of renal clearance was unaffected by the rate of urine flow. About 34% of the drug is bound to plasma proteins,[31] accounting for the fact that the clearance is less than that of the glomerular filtration rate. From 30% to 87% of a parenterally administered dose has been recovered in the urine of normal persons within 24 hours after injection.[71-74]

It has been frequently emphasized that, in the presence of uremia, streptomycin will accumulate in the blood if given repeatedly.[50,58,65,67,74,75] Kunin and Finland[50] studied the persistence of streptomycin in the blood of six severely uremic patients; the half-life of streptomycin in the serum of two anuric patients was 52.1 and 110.7 hours, respectively, and in two patients studied during the early diuretic phase of acute renal failure, the half-life was 51.8 and 75 hours, respectively. Two patients, studied while in the full diuretic phase, handled streptomycin differently: One of them was making a good recovery and was found to clear streptomycin with a half-life of 27.8 hours, while in the other patient (who later succumbed to intractable renal failure) the level in the serum fell only 50% during a period of 20 days after the last injection of the drug.

In view of these findings, one would expect the relation between streptomycin half-life in serum and glomerular filtration rate to be similar, although not identical, to that shown for Drug *A* in Figure 1 and for tetracycline in Figure 2.

Effect of Dialysis by the Artificial Kidney.—Edwards and Whyte[67] consider streptomycin toxicity to be an indication for hemodialysis by the artificial kidney in pa-

tients with severe renal disease, noting that the drug is dialyzable across a cellulose membrane. In their single case, in which measurement of streptomycin blood levels were reported prior to and on completion of dialysis, the concentration of drug in the blood fell from 32μg/ml. to 17μg/ml., but the patient subsequently developed signs of vestibular damage. This patient, however, was the only one to have developed toxicity among the eight patients who had been treated by dialysis specifically because they had received streptomycin.

Observations on the removal of streptomycin by the artificial kidney in one patient studied by the authors indicated an extraction ratio of only 24%, which is much less than would be expected for urea or creatinine. The fact that streptomycin is about 34% bound to plasma protein in vitro implies that dialysis by the artificial kidney would be of limited efficiency.

Thus, it would appear that streptomycin should be very sparingly used in uremic patients, particularly since other antibiotics are available which (in many instances) may serve equally well without similar potential danger. In the rare circumstance in which streptomycin must be used in a uremic patient, it may be advisable to take into consideration the half-life data reported above and to use an appropriate dosage schedule. The following is recommended:

A loading dose of 1 gm. should be given and followed by one-half the loading dose no more frequently than once every two to three days, and the drug should be stopped two to three days earlier than one would in the person with normal renal function.

Tetracyclines

Four tetracycline analogues are now available: tetracycline (TC), chlortetracycline (CTC), oxytetracycline (OTC), and the new one, demethylchlortetracycline (DMCT). TC has been the one that was most extensively used in this country because it produced less gastrointestinal irritation than either CTC or OTC and it penetrated well into the cerebrospinal fluid.[76-78] Each of the analogues, however, are potent drugs, and except for some differences in activity against certain species by one or another of the analogues and the feasibility of lower doses in the cases of DMTC,[79] they are virtually interchangeable for nearly all therapeutic purposes. Each of the earlier three analogues (DMTC has not yet had adequate study) produce, following prolonged therapy, morphologic and functional changes in the liver,[1-3,5-7] a negative nitrogen balance,[5-8] and increased riboflavin excretion into the urine.[6,8] Elevation of the blood urea nitrogen during OTC therapy has been reported by Womack et al.[80] and Bateman et al.[4] Farhat and co-workers[9] noted rising nonprotein nitrogen, anorexia, weight loss, lethargy, convulsions, and respiratory failure in rabbits given large doses of tetracyclines.

CTC is rapidly inactivated in serum and in alkaline solutions,[81-83] but the other tetracyclines are fairly stable under physiological conditions in vitro.[83,84] Differences have also been reported in the values for the persistence of tetracycline analogues in the blood and for the amounts recovered in the urine. Some of these differences may be due to errors inherent in the assay procedures, the relatively crude tube dilution methods and the more refined turbidimetric and cup-plate procedures used in the different studies. Thus, in one study in which the half-life of TC and DMTC in serum were compared, the two-fold dilution method was found to give consistently lower values than the cup-plate method.[79] Spitzy and Hitzenberger[85] employed a 2/3 serial dilution method and reported the half-life of tetracycline to be 2.08±0.66 hours following an intravenous injection of 100 mg. These results are at variance with calculations from data reported by others, who used the two-fold dilution method, which showed a half-life of 3 to 6.6 hours[86] and about 14 hours.[87] Andriola,[88] using an unspecified method of assay, presented data which indicates that the half-life in serum of TC was 7.5 hours.

Factors That Determine the Persistence of Antibiotics in Patients with Renal Disease *

Antibiotic	Renal Clearance		Parenteral Dose Recovered in the Urine, %	Bound to Plasma Proteins, %	Half-Life in Serum		References
	Rate †	Probable Mechanism ‡			Normal Subjects	Anuric Patients	
					Hr.	Hr.	
Penicillin G	560-1,080 ml/min.	G+T	58-85	48-58	0.5 #	7.2-10.5	42-45,50
Streptomycin	30-70 ml/min.	G	30-80	34	2.4-2.7	52-110	30,31,50,69-71,74
Tetracycline	62% of ^{c}creat §	G	60	24	8.5	57-108	32,34
Chlortetracycline	30%-37% of ^{c}creat	G	18	47-70	5.6	6.8-11.0	32,34,37
Oxytetracycline	85% of ^{c}creat	G	70	20	9.6	—	32
Demethylchlortetracycline	30% of ^{c}creat	G	42	41	12.3	—	32
Chloramphenicol: active-inactive conjugates	24 ml/min.	G	5-15	60	1.6-3.3	3.2-4.3	
	340 ml/min.	T	70-80	?	3.7-4.6	68.5-154.3	35,91,93,94
Erythromycin	76% of ^{c}creat (dogs)	G	15	?	1.4	4.8-5.8	50,105,106
Novobiocin	low	G	1.5-3.3	95	2.3	—	109-111,113,115
Bacitracin	159 ml/min.	?G	9-30.9 78.4-118.5	?	1.5 #	—	11,116
Kanamycin	81%-156% of ^{c}creat	G+?T	52-90	Low	3 #	—	118-121
Neomycin	?	G	30-50	Low	3 #	—	117,124
Polymyxin B	?	?G	?Large	?	6 #	—	17,132
Vancomycin	69% of ^{c}creat (dogs)	G	30-40 85-100	?	6 #	—	135,137-139
Ristocetin	67% of ^{c}creat (dogs)	G	79.4 (dogs)	?	—	—	141,142

* All data are for man except where otherwise specified.

† Divergent values for renal clearance and "half-life" were reported by Spitzy and Hitzenberger [40] for most of the antibiotics listed, and they are not included in this table.

‡ G=glomerular filtration; T=tubular excretion.

Approximate values.

§ ^{c}Creat=creatinine clearance.

Similar discrepancies have been found in the reports dealing with CTC and OTC.

Partly because of these discrepancies, Kunin, Dornbush, and Finland [32] carried out a comparative study in which the four tetracycline analogues were given intravenously and assays of antibiotic in serum were performed by the more reliable cup-plate assay method. A summary of the results of this study is included in the Table. The shortest half-life in serum was noted with CTC and the longest with DMTC, whereas TC and OTC yielded similar values which were intermediate.

The renal clearance and protein binding of CTC in man was studied by Sirota and Saltzman [37] using a fluorometric method of assay. They found that CTC was cleared by the kidney at a rate equivalent to 37% of a simultaneous creatinine clearance. From this and from their finding that CTC was about 70% bound to serum proteins, they concluded that the drug was cleared by glomerular filtration. The data on the clearances and binding of the four tetracycline analogues as determined by Kunin, Dornbush, and Finland [32] (shown in the Table) support the hypothesis of Sirota and Saltzman [37] that the tetracyclines are cleared by simple glomerular filtration and that the prime determinant of the rate of filtration is probably the degree to which each analogue is bound to plasma proteins.

In patients with renal disease certain differences are to be expected among the tetracycline analogues, in their persistence in the blood and in the amounts recovered in the urine. Thus, as pointed out in Figure 2, marked differences can be demonstrated in the half-life in serum of CTC and TC in patients with varying degrees of renal failure. The persistence of TC in the blood is markedly increased in the presence of renal failure, whereas that of CTC is vir-

tually unaffected by the presence of renal disease.[34]

Figure 4 is useful for estimating the concentration of each tetracycline that would be expected to appear in the urine for a given serum level in patients with varying rates of creatinine clearance. From this figure and the data presented in the Table, one may predict that, for a given serum level, OTC would appear in highest concentration in the urine followed closely by TC and then by DMTC, and rather low concentrations of CTC would be expected in the urine of uremic patients.

Figure 2 and the data shown in the Table may also be useful in planning dosage schedules for each analogue designed to achieve therapeutic levels of drug without the danger of accumulation.

It is evident from the data presented that the dosage of CTC in patients with renal failure should not be much different from that which is used in patients with normal renal function. The other three analogues, on the other hand, require adjustment of dosage in the presence of renal failure. Normally, OTC, because of its rapid rate of renal removal, should not persist in the blood as long as TC, whereas DMTC may be expected to persist somewhat longer than either TC or OTC.

Dialysis by the Artificial Kidney.—Tetracycline can be slowly removed from the body by means of hemodialysis with the artificial kidney.[34] The arteriovenous extraction ratio of this drug was found to range from 5% to 25%, or about 21% to 38% of creatinine extraction. No extraction of CTC by the artificial kidney could be detected in the single experiment in which this was attempted. The differences in the removal of these two analogues by the artificial kidney presumably reflects the extent to which they are bound to plasma proteins (Table). Efforts to remove TC from the blood by this method are limited by the low extraction rate, and this method is of no practical use in the case of CTC because of its rapid in vivo inactivation.

Chloramphenicol

Chloramphenicol is fairly stable in vitro, but in vivo it is inactivated,[89] primarily in the liver, by conjugation with glucuronic acid.[90-92] The active drug is excreted through the kidneys by glomerular filtration at a rate of about 24 ml/min.[91] This rate is presumably limited by plasma protein binding of about 60%.[91,93] The inactive glucuronide is cleared more rapidly by renal tubular excretion at a rate of about 340 ml/min.[91] Approximately 75% to 90% of the administered dose can be recovered in the urine, but only 5% to 15% of an administered dose appears in the urine in the unconjugated form.[91,94] The rate of conversion of chloramphenicol to its glucuronide is slower than normal in jaundiced patients who have cirrhosis of the liver[35] and in newborn infants in whom the glucuronic acid conjugating mechanisms are imperfectly developed.[95,96]

The occasional occurrence of depressed bone marrow function and the recently described "gray syndrome" in newborn infants during administration of excessive doses are the major complications of chloramphenicol therapy. The true incidence of bone marrow depression due to chloramphenicol is unknown. Three reports of nationwide surveys of severe reactions to antibiotics[97-99] revealed only a small number of cases considering the very large number of patients who had received the drug, but the true incidence could not be determined because data were not presented on the number of persons who had received chloramphenicol in the total population surveyed. However, there did not appear to be an increasing number of cases over the years.

Rubin et al.[100] suggested that chloramphenicol may produce subclinical bone marrow depression. In their studies, 5 of 15 patients who were receiving chloramphenicol showed reduced incorporation of iron into hemoglobin. After cessation of therapy, these patients showed an increased incorporation suggesting recovery from a

noxious substance. Although the possible role of renal impairment was not discussed by these authors, 3 of the 5 patients with reduced iron incorporation were listed as having renal disease, and 2 of the remaining 10 who showed no adverse effect from chloramphenicol are listed as having some disease of the kidney.

Newborn infants inactivate chloramphenicol slowly, presumably due to underdeveloped hepatic glucuronic acid conjugating mechanisms.[95,96] Since these infants also have incompletely developed renal function,[101] they tend to accumulate the active unconjugated drug. The cardiovascular collapse, or "gray syndrome" may be the result of retention of large amounts of active unconjugated drug, but mechanisms by which chloramphenicol exerts this effect are not clear.

Kunin, Glazko, and Finland[35] studied the persistence of chloramphenicol in the blood of patients with varying degrees of renal impairment, including several who were anuric. A summary of some of the results of this study is presented in Figure 3 and is also included in the Table. The normal half-life of antimicrobially active chloramphenicol is about three hours, and this was found to be unchanged by the presence of uremia. In this respect, active chloramphenicol resembles drug *B* presented in Figure 1. In contrast, the inactive derivatives of chloramphenicol (nitro compounds), which consist for the most part of the glucuronic acid conjugate, are retained in the blood for many hours in uremic patients. In this respect, the inactive compounds resemble drug *A* in Figure 1.

From the above considerations, it is mandatory (in order to achieve therapeutic effects) to use the same dosage schedule of chloramphenicol in patients with any degree of renal disease as would be used in normal patients with similar illnesses. It must be remembered, however, that the uremic patient will tend to retain the inactive products of chloramphenicol and that the potential toxicity of these products is unknown. It also must be pointed out that, since only 5% to 15% of the active drug is recovered in the urine of patients with normal renal function and the active drug is slowly excreted by glomerular filtration, it may be expected that smaller fractions of the administered dose would be excreted into the urine of uremic patients.

Dialysis by the Artificial Kidney.—The ability of the artificial kidney to remove chloramphenicol by hemodialysis is limited,[35] since it has been found that the active drug is extracted by the device only about one-third as well as creatinine and the metabolic products are removed about one-half as well. Since the active drug does not tend to accumulate in the blood of patients with renal disease anyway, and since the toxicity of the metabolic products is unknown, there does not at this time appear to be any important reason to attempt removal of these substances by hemodialysis.

Erythromycin

Erythromycin is a remarkably nontoxic drug when given in the usual therapeutic doses. Large oral doses, however, may produce diarrhea. Hypersensitivity, reactions have been occasionally reported.[102] Although the kidneys assume some significance in the removal of this drug from the body, nonrenal mechanisms are probably of greater importance. A considerable amount of erythromycin is excreted into the bile,[103,104] and only about 15% of an intravenously administered dose can be recovered in the urine of normal persons.[105] Lee et al.[106] determined the rate of clearance of erythromycin base in dogs and found it to be 65.4±5.7 ml/min/sq.m. body surface area, or 76% of the simultaneous creatinine clearance. Renal clearance data are not available for man.

Kunin and Finland[50] found the half-life in serum of intravenously injected erythromycin glucoheptonate to be about 1.4 hours in normal men and to be prolonged to 4.8 to 5.8 hours in anuric patients. Their data indicate that nonrenal factors must play

the most important role in the removal of the drug from the body.

The studies of Lee et al.[107] in rats suggest that at least some of the enhanced blood levels achieved with erythromycin propionate may be due to decreased biliary excretion. Griffith[108] was able to recover about 2.7% of erythromycin propionate in the urine as compared with 1.6% of the administered dose of erythromycin base. It is not clear as to whether the increased urinary recovery of the propionate is due to better absorption, delayed excretion into the bile, or increased removal of the drug by the kidneys. In any event, only relatively small amounts of the available erythromycin preparations are excreted into the urine.

From the data presented here, it appears that there is little tendency for active erythromycin to be retained in the blood of uremic patients. Thus, the dose used in the treatment of uremic patients should be substantially the same as in patients with normal renal function.

Novobiocin

The untoward effects of novobiocin therapy reported in the literature to 1957 for 1,189 patients treated with the drug were reviewed by Finland and Nichols.[109] They found that, on the whole, this antibiotic was well tolerated when given orally and that serious reactions from its use were remarkably few. Skin eruptions and drug fever were the commonest complications of therapy, being noted in 74 and 21 patients, respectively. Eosinophilia occurred in 15 patients while leukopenia was noted in only 7. Elevated icterus index and serum bilirubin levels were not accompanied by other evidences of disturbed hepatic function and could probably be attributed to a yellow pigment metabolite of novobiocin. These disturbances in color occurred at irregular intervals after the onset of therapy and frequently diminished as the therapy was continued. Impairment of renal function was not noted except for transient hematuria accompanying the rash and fever in two instances.

Novobiocin is highly bound to plasma albumin, but the binding is readily reversible. Simon et al.[110] found that 95% of the drug activity is lost in solutions containing 5% albumin. Martin et al.[111] and Jones and Finland[112] demonstrated that dilution releases drug activity from human serum. Spitzy and Hitzenberger[85] reported that the apparent volume of distribution of novobiocin was only about 13% of body weight, presumably because the greatest portion of the drug is bound to albumin in vivo and retained in the intravascular compartment. The rate of clearance by the kidney appears to be low since the ratio of the urine/serum concentration is also low (Fig. 4). Thus, in the study of Wright et al.,[113] this ratio was only 1.0-3.9. From analysis of the data of Martin et al.[111] and of Trafton and Lind,[114] more variable urine/serum concentration ratios are obtained ranging in those studied from 1:1.3 to 23:1 and from 1:3 to 44:1, respectively. Even in the latter studies, most ratios were low. These widely divergent results are not surprising in view of the great extent to which novobiocin is bound to albumin. As a consequence of the low rate of renal clearance of this drug, the total recovery in the urine has been reported to be consistently low. Simon et al.[110] recovered a mean of 1.5% of the drug in 24 hours: Wright et al.[113] recovered 2.7% to 3.3% in 72 hours: Spitzy[115] recovered 2% in 24-hour urine collections.

It would appear from these data that active novobiocin is removed from the body or largely inactivated by nonrenal mechanisms; that it is not nephrotoxic; that when used for therapeutic purposes in uremic patients, it should be given in essentially the same dose and at the same intervals as in patients without renal impairment.

Bacitracin

The systemic use of bacitracin, although a potent antibiotic against Gram-positive organisms, is ordinarily restricted to those

clinical situations in which the expected therapeutic results outweigh the potential renal toxicity. Protein, casts, and cellular elements appear in the urine on the second to third day of treatment with parenteral drug, reach a peak on about the fifth to seventh day, and usually decline somewhat as therapy is continued.[10,14] During the period of proteinuria, there is an acute depression of renal tubular function as evidenced by decreased clearance of PAH, tubular resorption of glucose and phosphate, and diminished rate of glomerular filtration. After cessation of therapy these functions may remain depressed for long periods, returning gradually to the baseline by seven to nine weeks.[11,12,14] Nausea and vomiting are the only other major untoward effects of therapy.

Meleney and Johnson[10] reviewed the status of bacitracin therapy up to 1953. They found that of 60 patients treated, 75% had only slight evidences of nephrotoxicity (as determined by the presence of albuminuria, and elevation of the BUN). In only two patients did they feel that toxicity was alarming, and in both of them it was reversible. From this experience and their review of other experiences with bacitracin, they recommended a maximum daily dose for adults of not more than 100,000 units and said that any single dose should not be larger than 25,000 units.

Bacitracin is excreted primarily by the kidney. Zintel et al.[11] recovered 9% to 30.9% of the administered dose in the first 24 hours after injection. Eagle et al.[116] recovered almost all of the injected dose of bacitracin in the urine within the first eight hours (78.4% to 118.5% of the dosage). The half-life of this antibiotic in blood, as calculated from their data, varied from 0.5 to 2.3 with a mean of about 1.5 hours for doses ranging from 1.1 to 5 mg/kg. of body weight. These workers found that the renal clearance of bacitracin in nine human subjects varied from 105 to 283 ml/min., averaging 159 ml/min., or about 1.1 times the rate at which sodium thiosulfate was cleared. They concluded that the mechanism of renal clearance of bacitracin was not clear from their studies but that it was possibly excreted by glomerular filtration alone. If bacitracin is indeed removed at this rate by glomerular filtration alone, it may also be efficiently removed by hemodialysis with the artificial kidney. This possibility should be kept in mind for the rare situation of a uremic patient in which it may be desirable to remove the drug from the blood rapidly.

Despite the profound and general depression of renal function produced by bacitracin it is still a useful antibiotic, particularly when properly used systemically in serious staphylococcal infections or topically in many infections with Gram-positive organisms. Fortunately, the renal damage produced by bacitracin is usually reversible. Its use in uremic patients, however, must be undertaken, if at all, with extreme caution since (1) it is largely excreted by the kidneys and may accumulate when given repeatedly in patients with renal failure, (2) even small reductions in renal function may threaten life for patients with renal disease, and (3) other drugs can frequently be found that are as effective and less dangerous.

Neomycin and Kanamycin

These antibiotics are considered together because of their chemical, antibacterial, and pharmacological similarities.[23,24] Kanamycin has largely replaced neomycin for parenteral therapy because it appears to produce less auditory and renal damage. Both drugs are poorly absorbed from the gastrointestinal tract and are used orally for intestinal antisepsis, preoperatively, and in patients with hepatic coma. They are water soluble bases, stable in vitro, and have low affinity or binding to plasma proteins. Their half-life in serum is about three hours after intramuscular injection in patients with normal renal function.[117-119]

The mode of excretion of neomycin has not been extensively studied, but it appears

to be similar to that of kanamycin. Boger and Gavin [120] found kanamycin to be cleared by the kidneys at a rate of 81% of a simultaneous creatinine clearance and were unable to demonstrate any significant change in this rate following the concomitant administration of probenecid. Somewhat higher rates of clearance were reported by Berger et al.[121] in children; the clearance values obtained by these workers ranged from 118% to 156% of the creatinine clearance. The latter authors favored the hypothesis that some tubular secretion of kanamycin occurred to account for these high values.

Following parenteral injection in dogs and man, both neomycin and kanamycin are rapidly excreted. Todd and Wright [122] recovered 49%-88% neomycin, and Tisch et al.[123] recovered 27%-88% kanamycin in the urine of dogs after a single injection. Following intramuscular injection of kanamycin in man, Welch et al.[118] recovered 52%-73% and White and Knight [119] recovered 54% of the administered dose in the urine; Bogen [124] reported 30%-50% urinary recoveries of neomycin under similar conditions.

Although the absorption of these drugs from the gastrointestinal tract is poor, they cannot be considered as strictly "nonabsorbable" antibiotics. Freyburger and Johnson [125] recovered 3%-6% of an oral dose of neomycin in the urine of dogs, and Poth et al.[126] recovered 3% in man. Kunin et al.[127] recovered 0.6% and 0.7% of orally administered doses of neomycin and kanamycin, respectively, in the urine of man. Serum levels of 1.25μg/ml. and 3.0μg/ml. of neomycin have been reported after oral administration by Waisbren and Spink [128] and Poth et al.,[126] respectively. Cohn [129] was unable to detect kanamycin in the blood of patients receiving 4-6 gm. orally per day in specimens drawn four hours after the last oral dose. Finegold,[130] from personal observations and from other reports, noted serum levels up to 5μg/ml. and urine levels up to 256μg/ml. in patients receiving oral kanamycin. Kunin et al.[127] found low blood levels (1μg.-9μg/ml.) of both neomycin and kanamycin in cirrhotic patients without renal disease receiving 8-12 gm. orally per day. Of considerable interest is the finding that patients with renal disease tend to retain the small amounts of drug absorbed from oral doses and, in some instances, attain levels of antibiotic in the blood comparable to those achieved with parenteral therapy.[131] The gradual build-up of antibiotic in the blood in such patients was most marked with neomycin, but fewer uremic patients receiving kanamycin have been studied.[127]

The nephrotoxicity and ototoxicity of neomycin and kanamycin are well documented,[15,23,24] and these may be increased in patients with impaired renal function.[131a,131b] Since both drugs are largely excreted into the urine, and since it has been demonstrated that kanamycin [50] and neomycin [127,130,131] may accumulate in the blood of patients with renal disease, it would appear prudent to reduce the dose of both (whether given orally or parenterally) in patients with renal failure. As in the case of patients with normal renal function, it would appear that kanamycin would be a more desirable drug to use in patients with renal disease than neomycin because of its lower toxicity. It may be wise to carry this reasoning over to oral therapy when the patient has renal failure for the reasons given. Concentrations of kanamycin in the urine of uremic patients who are not anuric should be relatively high because of the rapid rate at which this drug is cleared by the kidneys,[120,121] and therefore, when given cautiously, it may be useful in specific urinary tract infections—even in patients with mild renal failure.

Polymyxin B

Of the five polymyxins (A through E), only polymyxin B is now in general use and will be considered here. The literature was reviewed in 1949 by Stansly [132] and again, in 1956, by Jawetz.[15] Aside from

local irritation and pain at the site of injection, the major untoward results of therapy with polymyxin B are its nephrotoxic and neurotoxic effects and drug fever. The commoner neurologic effects of polymyxin B therapy are transient paresthesias, hyperesthesias, weakness, drowsiness, dizziness, and ataxia; all of which progress if the treatment is continued. Like the nephrotoxic effects, these occur more readily in patients with previous renal disease and appear to be dose-related. The nephrotoxic effects appear to be less marked with polymyxin B and E than with A and D.[19] In patients with normal renal function given a daily dose of 2.5 mg/kg. body weight or less, either no change or only minimal changes in renal function have been noted even after one to two weeks of therapy. When larger doses are given, although they usually do not appear necessary for optimum results, protein, casts, and cellular elements appear in the urine, and nitrogen retention develops.[16,19,22] Patients with pre-existing renal disease on a daily dose of 2.5 mg/kg. may develop impaired glomerular and tubular function even after a few days of therapy[16,20,22]; for that reason, it is recommended that such patients should not receive more than 1-2 mg/kg/day.

Polymyxin B is slowly excreted into the urine, but the exact rate and mode of excretion, and even the total amount recovered in the urine, have not been clearly defined. For example, the figure frequently given that 60% of the administered dose may be recovered in the urine within 72 to 96 hours refers to polymyxin D rather than to polymyxin B.[18,132] Pulaski and Rosenberg,[133] using polymyxin B, found that during the first 12 hours less than 0.1% of the injected dose appeared in the urine, but after that progressively increasing amounts were excreted. On a daily dose of 3 mg/kg., urine concentrations of 40μg.-400μg/ml. were found, but no data on the total recovery were given. Presumably, the delayed appearance of the drug into the urine reflects slow absorption and distribution from the injection site.

With daily intramuscular doses of 2-4 mg/kg., serum concentrations are usually 1μg.-8μg/ml. The peak level occurs 30 minutes to 2 hours following injection; one-half the peak level is noted at 6 hours, and the drug can be detected in the blood up to 12 hours.[17] No drug accumulation is ordinarily noted when injections are spaced at 12-hour intervals, but this may occur when the drug is given more frequently. Jawetz and Coleman[16] reported that almost all activity disappears from the blood of patients with normal renal function by 6 to 8 hours after a dose, but even on doses of 20 mg. every 8 hours measurable levels could be detected in the blood of uremic patients at 18 to 24 hours after the last dose. They found that blood levels of 2μg.-5μg/ml. usually could be maintained in uremic patients given 20 mg. every eight hours. Serum levels up to 15μg/ml. have been noted in patients with marked nitrogen retention who received daily doses of 100-150 mg. of polymyxin B for one week.

It would therefore appear that polymyxin B can be given to patients with normal renal function with reasonable safety when the dose is no greater than 2.5 mg/kg/day. Patients with renal disease tend to accumulate the drug and are likelier to develop nephrotoxic and neurotoxic effects, even after short courses of therapy. Because of the almost unique effectiveness of polymyxin B against Pseudomonas aeruginosa, there are times when this drug may be lifesaving if it is given for short periods, even to patients having impaired renal function. Rather than use the doses recommended by some authors and noted above for patients with renal failure, it may be preferable to give the usual dose for the first two to three injections in order to achieve high blood and tissue levels early; therapy should then either be stopped or sharply reduced.

A new polymyxin antibiotic, Colimycin,* that is currently under investigation is also effective against strains of Pseudomonas.

* Recently given the generic name "colistin."

Early studies [134] suggest that this drug may be less nephrotoxic than polymyxin B, but there are inadequate reports of its use in patients with renal disease to warrant conclusions as to its relative value in such patients.

Vancomycin

The early lots of vancomycin were relatively impure and produced phlebitis, drug fever, and renal irritation in some cases. Recent lots of the drug are somewhat better tolerated, but phlebitis has remained troublesome, particularly since intravenous injection is the only effective mode of systemic administration. Drug fever and occasional rashes are reported, but toxic renal, hepatic, and hematologic effects have not been noted.[135,136] The most serious toxic effect, however, is deafness, which has been observed during or soon after treatment in a few patients, some of whom had renal failure with nitrogen retention.[26,27,136]

The half-life in blood is about 6 hours,[135] and some tendency toward accumulation has been reported for doses given at the generally recommended 6 to 12 hour intervals.[137] Excretion into the urine appears to be the most important route by which vancomycin is removed from the body. The total recovery of the drug in the urine has been variously reported as 30%-40%,[138] and 85%-100% [137] of the administered dose by two different groups of investigators. The rate and mode of excretion into the urine has not been reported for man but appears to be relatively slow, since 24 hours after a single intravenous injection of 500 mg., concentrations of about 100μg/ml. in the urine have been reported.[135] Dogs given intravenous vancomycin cleared the drug at a rate that was 69% as rapid as that of creatinine.[139]

Vancomycin tends to accumulate in the blood when given repeatedly to patients with renal disease. Thus, one patient whose BUN was 40 mg. % was found to have 5μg/ml. of vancomycin nine days after therapy had been discontinued, and another patient whose BUN ranged from 40 to 50 mg. % had levels of 100μg/ml. of blood on three occasions 12 hours after previous doses.[137] The higher levels have been associated with deafness in some cases.[26,27]

Ristocetin

Thrombocytopenia and neutropenia are the most serious complications of ristocetin therapy [140-144]; phlebitis, rash, and drug fever may also be troublesome.[141-143,145] The hematologic complications appear to be dose-related, since (for the most part) they have been noted when large doses have been used or in patients with renal failure who tend to retain and accumulate the drug.[140-144] For example, two of the three cases of acute thrombocytopenia believed to be due to ristocetin occurred in uremic patients.[141]

Data on the renal clearance and recovery of the drug in the urine of man have not yet been reported. Romansky is quoted by Gangarosa et al.[141] as having found that "more than half a given dose is retained in excess of 24 hours." In the dog, 79.4% of the administered dose was recovered in the urine and the drug was cleared 67% as rapidly as creatinine.[146] Plasma protein binding determinations have been difficult to perform because ristocetin diffuses very slowly across cellophane membranes.[146]

From the information thus far available, particularly with regard to toxic effects, it would appear advisable to use ristocetin with considerable caution in patients with renal failure.

Summary and Conclusions

Relatively simple pharmacological principles have been applied to the problem of the restrictions that may be imposed by renal failure on antibiotic therapy.

The results of determinations of blood levels of antibiotics may serve as a useful guide to the need for such restrictions. The size and frequency of doses which may properly be used in patients with impaired renal function depend largely upon the elimination rate constant and the apparent volume of distribution of the drugs.

For drugs that are excreted largely by the kidneys, the elimination rate constant of an antibiotic is decreased, and the related "half-life" of the antibiotic in the blood is markedly prolonged in patients with renal failure. The exact change in these rate measurements that are produced by any given antibiotic as a result of renal failure can be estimated, but it is best determined empirically for each drug.

In general, the more rapidly a drug is cleared by the kidney, the likelier it is to appear in the urine at therapeutic levels (in spite of renal failure) when the levels in the blood are at the usually desired concentrations.

Some of the factors which influence the limitations imposed by renal failure are outlined in detail for the commonly used antibiotics, and these are summarized in the Table.

It is hoped that the principles and data reviewed here will serve as useful guides to antibiotic therapy in patients with anuria or with severe but lesser degrees of renal functional impairment.

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Books

EDITED BY WILLIAM B. BEAN, M.D.*

Essays in Philosophical Biology. By William Morton Wheeler. Price, not given. Pp. 260, with 4 illustrations. Harvard University Press, Cambridge 38, Mass., 1939.

I have not hesitated to review books published some time ago if their message still rings true today: Nor have I excluded a book from consideration just because it was out of print. Since nonmedical books may have much value for the internist or general physician, such books are brought up from time to time. My purpose in this review is to introduce one of my favorite people, the late William Morton Wheeler, a thinker of heroic proportions as well as a scholar in taxonomy and ecology. If, in browsing around old book stores, you come across any of his essays, addresses, or even any of his treatises, on ants, seize them and treasure them, for Wheeler is full of rare savor and rich rewards.

The study of ants has a way of attracting remarkable people. At least, this is my experience with zoologists I have known personally. Of those not known first hand, the names of Fabre, Maeterlinck, and Wheeler come to mind. Either the study of ants attracts people with curious insights or it encourages those insights to grow and develop in an unusual way. Perhaps the most remarkable of all the ant lovers was William Morton Wheeler. Not only did he make a tremendous impression on those who knew him but his essays and speeches recorded in this volume catch his piquant irony, his directness, and his ability to see through humbug in getting to the heart of any problem. Though his scientific reputation is built on his artistry in taxonomy and his erudition in ecology, there were other major contributions which make it important to bring his name and his work before this generation of physicians who, for the most part, have never heard of him. His colleagues admired his omnivorous, vast, and varied reading, his knowledge of the classics, and his exhaustive familiarity with modern foreign languages—including many technical aspects of their structure and their idioms. He had a freshness in writing, almost unique in biology and medicine. He was groundedly learned. His versatility, combined with an exquisite sense of humor, deflated many a stuffed shirt and pricked many a bubble with gentle irony, pungent critique, or penetrating ridicule. He could detect bombast and cant and was their natural enemy. He used the term "flub-dub" for sham, pedantry, and self-aggrandizement, which he attacked more violently than he did some of man's baser attributes. Another one of his pet abominations were the "wowsers," a word he used to designate "an individual who makes a business of taking the joy out of life, one who delights in pouring cold water into his own and especially into other people's soup." The term appears to be onomatopoeic to judge from a remark he ascribed to Wee-Wee, king of the termites (one of the postcretaceous philologists), who asserted that, "Whenever the wowser saw termites dancing, swearing, flirting, smoking or overindulging in the social hormones, he sat up on his hind legs, looked very solemn, swelled out his abdomen and said, 'Wow!'"

As a great naturalist with formal training in zoology, he was able to advance both as a doer and thinker, a practitioner and theorist. He was a great teacher, a speculative philosopher, a man with learning which could only be called encyclopedic. His intense concentration and his swift recognition of significant patterns in the classification of insects carried over into his judgment of men and affairs. An incredible amount of hard work had gone into building up his knowledge. His reading was broad and deep, including the literature of many languages. His writing shows a devotion of literary excellence, fine perception, and an exquisite style. His use of irony and gentle satire reminds us more of Voltaire than Swift. An abiding sense of humor kept him from developing pomposity and pedantry. Perhaps it is a sufficient tribute to recall that White-

* Communications to this Department may be sent directly to Dr. William B. Bean, University Hospitals, State University of Iowa College of Medicine, Iowa City, or to the Chief Editor for transmittal to him.

head characterized him as the only man he had ever known who would have been both worthy and able to sustain a conversation with Aristotle.

All too often the death of a great man extinguishes not just his career but the living synthesis and accumulation of experience, judgment, skill, and knowledge, which can hardly be transmitted. Nonetheless, the savor of the man can be gained from reading the delightful collected essays.

It is hard to single out any one of the dozen essays in this collection for special praise. My favorite happens to be the one entitled "The Termitodoxa, or Biology and Society," which was originally published in the *Scientific Monthly* in February of 1920. The letter, from the king of the *Termes bellicosus* tribe of termites in West Africa, Wee-Wee, by name (the 43rd Neotenic King of the 8429th Dynasty of the Bellicose Termites), is a classic essay which everyone should know. It is difficult to quote any part of it. You must read the whole. I conclude by saying that this is vintage satire, increasing its bouquet, savor, and fragrance with aging and producing a sense of admirable warmth and well-being. Its addicting qualities are strong but fortunately healthful.

WILLIAM B. BEAN, M.D

Transactions of the Eighteenth Conference on the Chemotherapy of Tuberculosis. Prepared and edited by the VA Department of Medicine and Surgery, Central Office, Washington, D.C., and the St. Louis area Medical Office. Price, not given. Pp. 479, with many tables and figures. U.S. Veterans Administration, Department of Medicine and Surgery, Washington 25, D.C., 1959.

The Veterans Administration Department of Medicine and Surgery, the three Armed Forces, and several other organizations have engaged in a well-coordinated cooperative study of the chemotherapy of tuberculosis since the close of World War II. The 18th Conference was held in St. Louis, in February, 1959. This paper-bound volume is a complete transcript of fifty papers presented there along with spontaneous discussions and comments—sometimes of more worth than the formal presentations—thirty-one papers read by title, and committee reports which deal largely with future study plans. This conference had world-wide representation and can be expected to continue to exert a major influence in tuberculosis practice.

The Transactions are devoted chiefly to drug therapy for tuberculosis—primarily pulmonary, of course—but they touch on several extra-thoracic forms of the disease as well. Other modalities of treatment, especially resectional surgery, receive attention. Several good papers are devoted to laboratory methods and the bacteriology of the tubercle bacillus as well as mycobacteria, variously described as "unusual," "atypical," "anonymous," and "saprophytic." There is a good section on coccidioidomycosis which has now been incorporated into a cooperative study of its own.

No new drugs are announced and no startling advances in knowledge regarding the older ones are presented, but there is much necessary and valuable confirmation and clarification of information previously presented in the vast new field of tuberculosis therapy. Especially well defined are: (1) The roles of our "front-line" agents, isoniazid and streptomycin, and the second- or third-rate drugs such as aminosalicylic acid (PAS), cycloserine, and viomycin; (2) duration of drug treatment; (3) the place of steroids in tuberculosis; (4) principles governing thoracic surgery for tuberculosis; (5) principles governing management of genitourinary tract tuberculosis.

The Transactions are invaluable for the specialist in chest diseases and contain much of value for the general internist, but they are perhaps too lengthy and detailed to be of more than limited value to physicians in other categories of practice.

CHARLES W. GRAY, M.D.

An Atlas of Normal Radiographic Anatomy. Second edition. By Isadore Meschan, M.A., M.D., and R. M. F. Farrer-Meschan, M.B., B.S., M.D. Price, $16.00. Pp. 759, with 1446 illustrations in 412 figures. W. B. Saunders Company, 218 W. Washington Sq. Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1959.

This is the second edition of a book which can be found in most radiology departments, especially where there are residents in training. The general outline is the same as for the first edition, with the body being radiographically dissected, section by section. The basic projections utilized in radiography are demonstrated along with a reproduction of the radiograph thus obtained and labeled line tracings. The presentation is clear and concise, and reproductions are excellent throughout.

The section on the heart and major blood vessels has been greatly expanded to include angiocardiography and abdominal aortography, keeping pace with greater surgical interest in these areas. Cerebral angiography and myelography also receive greater emphasis.

A new chapter dealing with the protection problems involved in roentgenology has been introduced. It is brief, almost to the point of confusion, but presents current thought on permissible dose ranges. An outline of controllable factors is also presented for protection of the patient and physician.

Although the book will probably be of greater interest to the radiologist, it is highly recommended for all medical students and physicians who would have a better concept of diagnostic roentgenology.

EUGENE VAN EPPS, M.D.

The Year Book of Endocrinology (1958-1959 Year Book Series). Edited by Gilbert S. Gordan. Price, not given. Pp. 384, with 87 illustrations. The Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1959.

Twelve months ago, Gordan wrote this in his introduction to the 1957-1958 volume. "It is the intention of this volume to depict the endocrine literature, albeit in miniature. The articles selected for abstracting and presentation have been chosen because, in the opinion of your editor, they represent what is being reported. This is not a text book of endocrinology, and this year's literature does not necessarily cover every pertinent field, for which the interested reader is referred to one of the numerous excellent texts published in the past few years. Parenthetically, let me add that a particular effort is made to search out those articles which are not generally available in the Journals received by most American physicians. . . . Pertinent articles in all languages can be and are considered for inclusion here." Gordan has succeeded annually, and the current Year Book of Endocrinology is of the highest quality. It is recommended to all physicians, specialized or not. It gives "all the breath and the bloom of the year in the bag of one bee." One cavil: A number of the case histories start, "Girl, 17, developed . . ." or "Man, 24, showed. . . ." This ugly omission of the "A" is not followed throughout the case histories. At least one regular reader would like to see the indefinite article.

DANIEL B. STONE, M.B.

Ciba Foundation Symposium on the Regulation of Cell Metabolism. Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch., and Cecilia M. O'Connor, B. Sc. Price, $9.50. Pp. 387, with 109 illustrations. Little Brown & Company, 34 Beacon St., Boston 6, 1959.

The symposium that constitutes this edition deals primarily, but not exclusively, with "primitive" control mechanisms of the cell. Hormonal influences are not extensively treated.

Sixteen papers and discussions by prominent research workers are presented at the biochemical level, describing many ideas and problems on the regulation of cell metabolism. Among the substances and mechanisms considered in the papers as playing a regulatory role in cell metabolism are the intracellular concentration of inorganic phosphorus, adenosinediphosphate, enzyme concentration, electron transport, coenzymes, and a "feed-back" concept.

This book is by experts, primarily for experts, in this field.

ROBERT T. MARSHALL, M.D.

News and Comment

ANNOUNCEMENTS

Fourth National Cancer Conference.—The Changing Concepts Concerning Cancer will be the theme of the Fourth National Cancer Conference, sponsored by the American Cancer Society and the National Cancer Institute, to be held in Minneapolis, Sept. 13-15, 1960.

For further information, write to the Medical Affairs Department, American Cancer Society, 521 W. 57th St., New York 19.

GENERAL NEWS

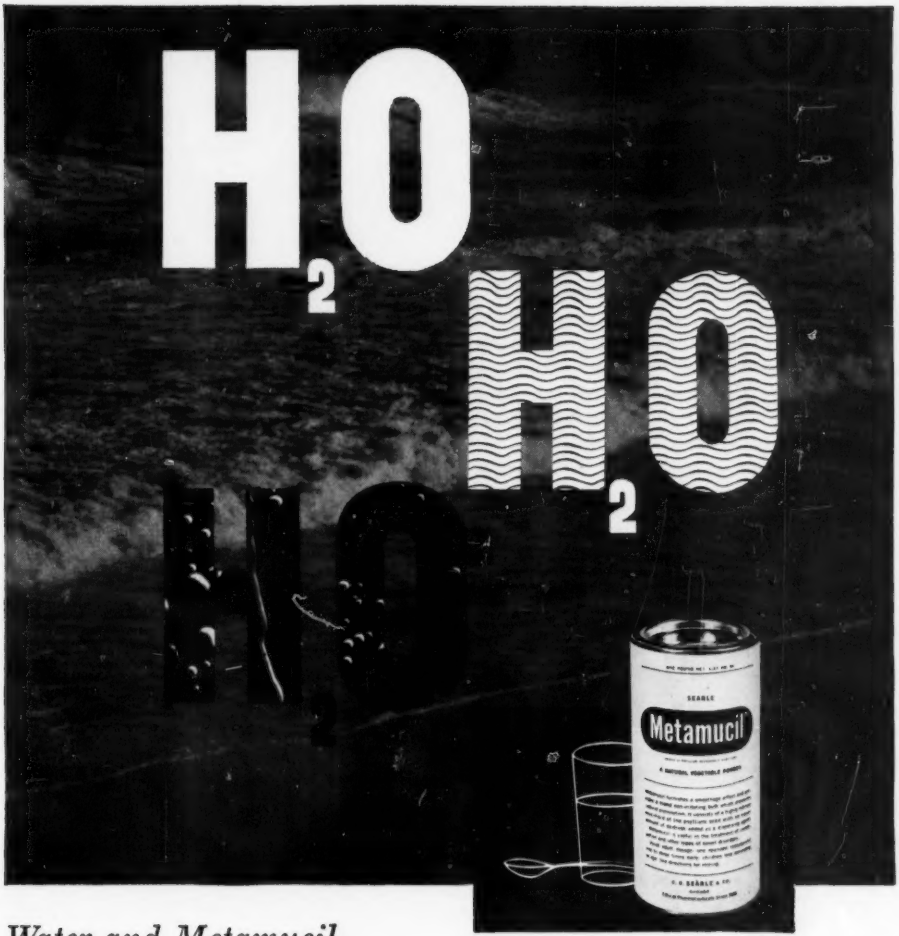
New Clinical Center Study on the Stein-Leventhal Syndrome.—An investigation of the role of the adrenal gland in the Stein-Leventhal syndrome has been initiated at the Clinical Center, National Institutes of Health. Salient features in this syndrome include oligomenorrhea, hirsutism, and polycystic ovaries.

The cooperation of interested physicians in referring laparotomy-proved cases is invited. Referral letters or phone calls will receive prompt attention and should include detailed medical information about the patient.

Accepted patients will be studied for varying periods up to several weeks. Upon completion of their study, patients will be returned to the care of their referring physician, who will also receive a detailed narrative summary. In some instances it may be desirable to arrange for occasional follow-up visits to the Clinical Center. These would supplement rather than substitute for visits to the patient's own physician.

Physicians interested in the possibility of referring patients should write or telephone J. E. Rall, M.D., Chief, Clinical Endocrinology Branch, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md. (OLiver 6-4000, Ext. 4181) or Saul W. Rosen, M.D., Clinical Associate, National Institute of Arthritis and Metabolic Diseases, Bethesda 14, Md. (OLiver 6-4000, Ext. 2936).

Arthropod-Borne Encephalitis.—The National Library of Medicine has just issued a bibliography on arthropod-borne encephalitis. Copies may be obtained, at no cost, upon request to the Acquisition Division, National Library of Medicine, 7th St. and Independence Ave., S.W., Washington 25, D.C.



Water and Metamucil

Both are basic for relief and correction of constipation

Effective relief of constipation and actual correction of the condition depend on an intake of a sufficient quantity of water to facilitate movement of the fecal mass in the bowel lumen. Also useful is Metamucil which adds a soft, bland bulk to the bowel contents to stimulate normal peristalsis and also hold water within stools to keep them soft and easy to pass. Thus Metamucil and an adequate water intake induce natural elimination and promote regularity.

Metamucil®

brand of psyllium hydrophilic mucilloid

SEARLE

A well-balanced moderate low-fat breakfast for teen-age girls, 16-19 years

When a moderate reduction of dietary fat is indicated for girls in their late teens, the basic cereal and milk breakfast merits consideration. *This breakfast is moderately low in fat because its fat content of 10.9 gm. provides 20 per cent of the total calories.* As shown in the table below, it contributes *well-balanced nourishment.* It provides "Girls, 16 to 19 Years" with approximately one-fourth of the recommended dietary allowances[1] of complete protein, important B vitamins, essential minerals; and provides quick and lasting energy.

recommended dietary allowances and the nutritional contribution of a moderate low-fat breakfast*

Menu: Orange Juice—4 oz.;
Cereal, dry weight—1 oz.;
Whole Milk—4 oz.; Sugar—1 teaspoon;
Toast (white, enriched)—2 slices;
Butter—5 gm. (about 1 teaspoon);
Nonfat Milk—8 oz.

Nutrients	Calories	Protein	Calcium	Iron	Vitamin A	Thiamine	Riboflavin	Niacin equiv.	Ascorbic Acid
Totals supplied by Basic Breakfast**	503	20.9 gm.	0.532 gm.	2.7 mg.	588 I.U.	0.46 mg.	0.80 mg.	7.36 mg.	65.5 mg.
Recommended Dietary[1] Allowances—Girls, 16 to 19 Years (54 kg.—120 lb.)	2400	75 gm.	1.3 gm.	15 mg.	5000 I.U.	1.2 mg.	1.9 mg.	16 mg.	80 mg.
Percentage Contributed by Basic Breakfast	20.9%	27.9%	40.9%	18.0%	11.8%	38.3%	42.1%	46.0%	81.9%

**Revised 1958. Food and Nutrition Board, National Research Council, Washington, D.C.*

***Cereal Institute, Inc.: Breakfast Source Book. Chicago: Cereal Institute, Inc., 1959.*
Watt, B. K., and Merrill, A. L.: Composition of Foods—Raw, Processed, Prepared. U.S.D.A. Agriculture Handbook No. 8, 1950.

[1]The allowance levels are intended to cover individual variations among most normal persons as they live in the United States under usual environmental stresses. Calorie allowances apply to individuals usually engaged in moderate physical activity. For office workers or others in sedentary occupations they are excessive. Adjustments must be made for variations in body size, age, physical activity, and environmental temperature.

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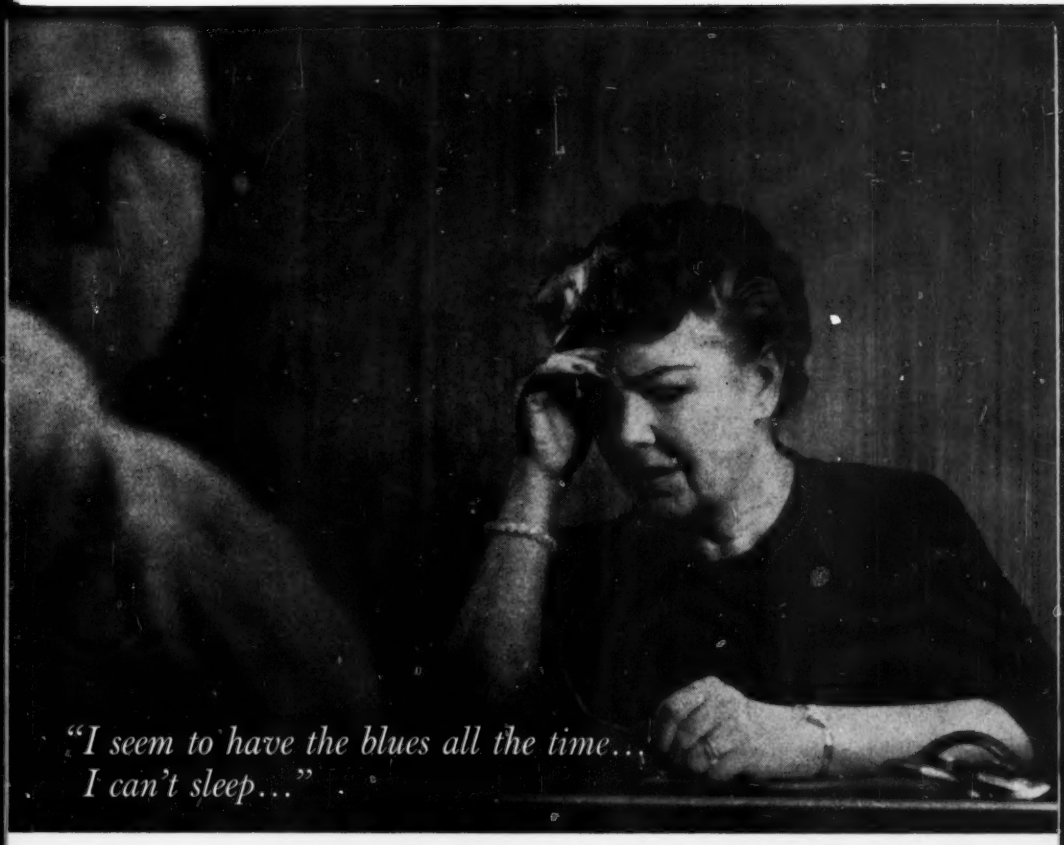

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Composition: Each light-pink, scored tablet contains 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate.

for depression

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References:
1. Alexander, L.: J.A.M.A. 166:1019, March 1, 1958.
2. Current personal communications; in the files of Wallace Laboratories.
3. Pennington, V.M.: Am. J. Psychist. 115:250, Sept. 1958.

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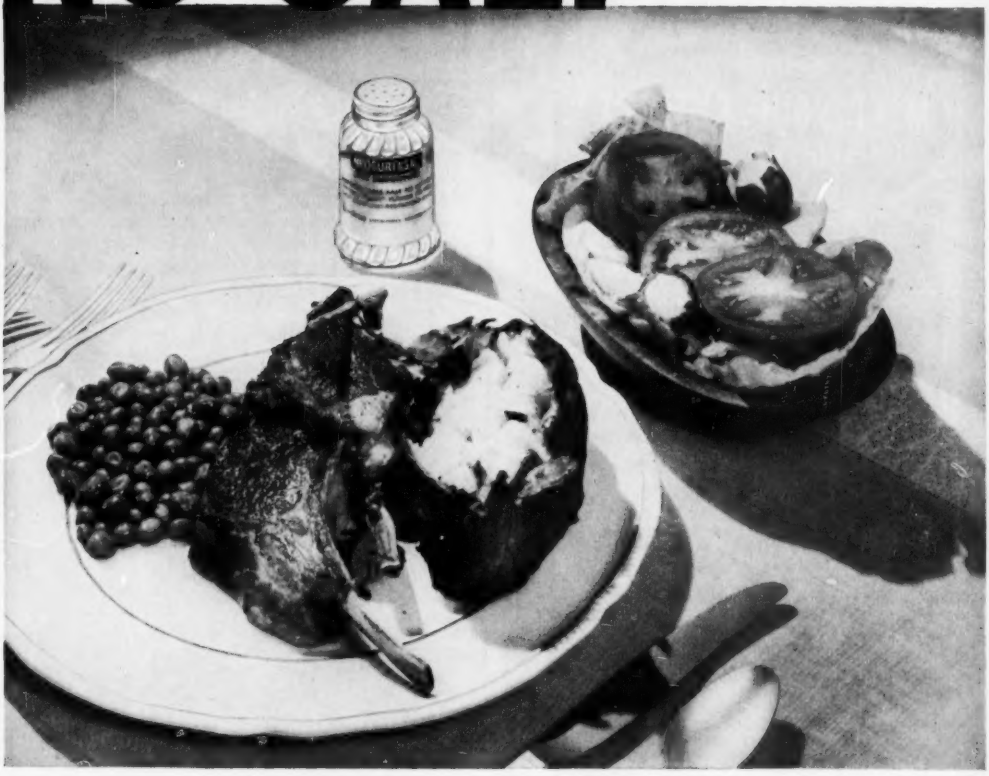

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Malt Soup Extract Powder is specially processed non-diastatic barley malt extract neutralized with potassium carbonate.

Two heaping tablespoonfuls twice a day is the usual effective dose and this may be reduced to two tablespoonfuls at bed time when satisfactory results are secured.

Malt Soup Extract is available in liquid and powder form in 8 oz. and 16 oz. jars at most drug stores coast to coast.

*Diseases of the Colon & Rectum, Vol. 1, No. 5, Sept.-Oct. 1958.

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In Nutrition...

2+2=5

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Which is another way of saying that fat, protein, carbohydrate, vitamins and minerals in food work more effectively together than when isolated and alone. Some nutrients are limited, others are ineffective when eaten alone. A diet of food is better than a diet of purified substances found in food.

Recognition of this principle led to the discovery of vitamins. It is also dramatically demonstrated in the phenomenon of the sparing effect of flour added to a purified amino acid ration.

In studies of human amino acid requirements at the University of Nebraska,* it was found that a few subjects persisted in constant, negative nitrogen balance *on the same diet* of purified amino acids that kept others in equilibrium. Even after two to four weeks, these subjects could not satisfy their protein needs on the purified diet. But within 24 to 48 hours after wheat flour was substituted as a source of some of the crystalline amino acids, a marked nitrogen retention occurred.

The intake of amino acids was in no way changed—only the source of the amino acids. The ration with flour added proved to be a more nutritionally effective source of protein.

Translate the Nebraska research into terms of daily practice. Consider succulent meat eaten between slices of enriched bread—the ordinary but much-loved sandwich. You might say you were eating an effective protein combination, amino acids of cereal and animal origin supplementing each other—plus fat, carbohydrate, vitamins and minerals. But more likely, you would simply exclaim-"Mmm-good!"

And "good" is the word for sandwich—good nutritionally and good for eating. For man does not live by bread alone . . . nor by meat, milk, fruit or vegetables alone. The best advice in nutrition is to eat a varied, balanced, *enjoyable* diet of all foods.

But advice is one thing; what people do, another. If you are devoted to good community nutrition . . . if you want to help people you meet professionally with their personal food problems, may we send you for review our special Nutrition Project Kit of authoritative materials?

*Proceedings of the Nutrition Symposium Series, No. 8, Symposium on Protein Metabolism. New York, National Vitamin Foundation, Inc., March, 1954.

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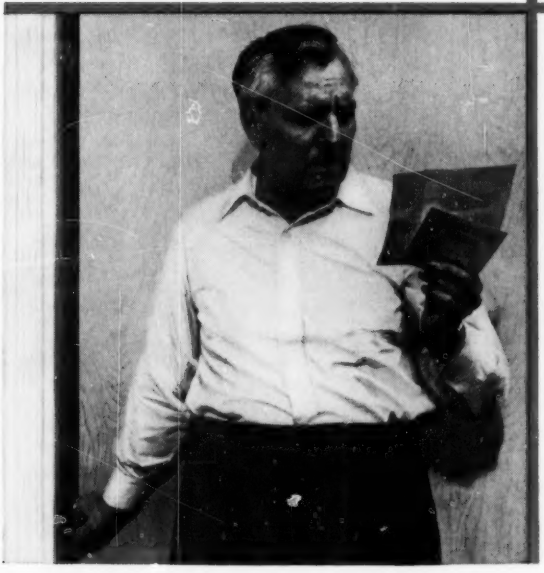

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References: 1. McDermott, W. V., Jr.; Waisman, J., and Riddell, A. G.: New England J. Med. 253:1065 (Dec. 29) 1955. 2. Watson, D.: A.M.A. 166:764 (Feb. 15) 1958.

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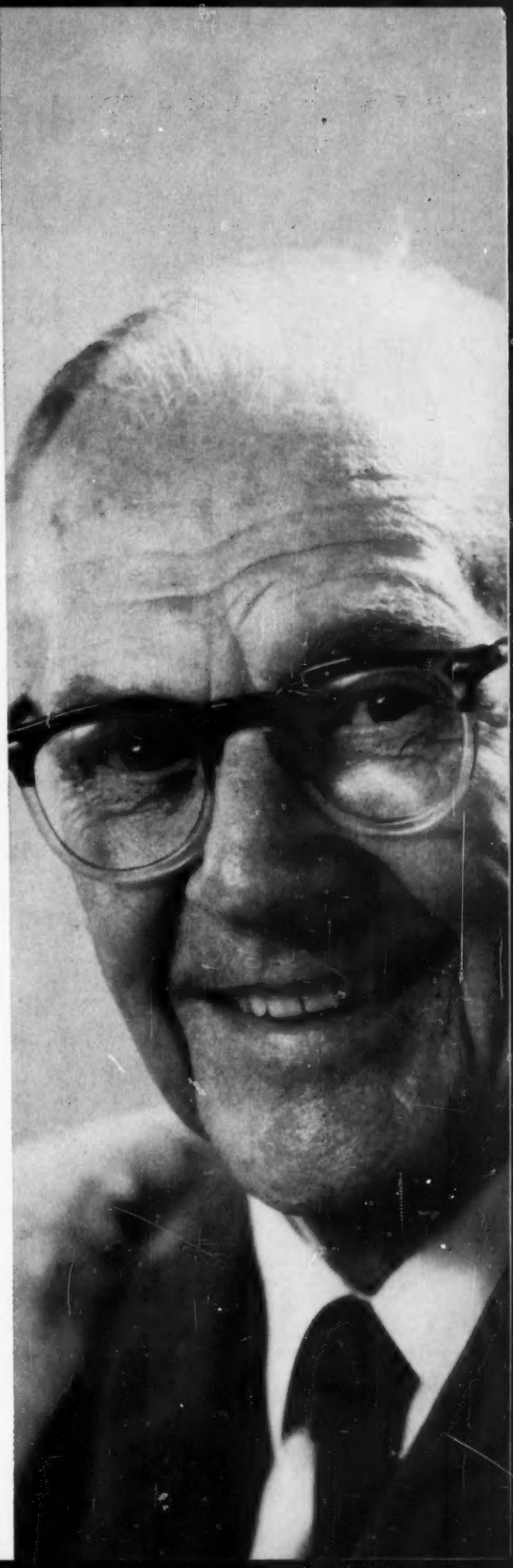
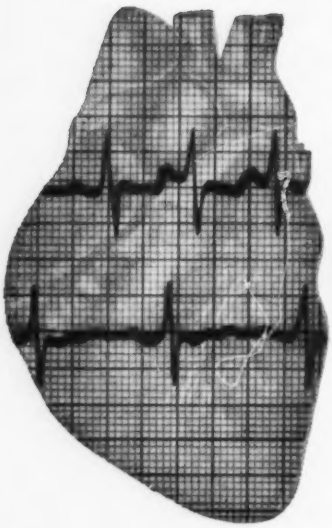


in atrial fibrillation

suitable for conversion



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1. Smith, J. M.: Lederle Bull. Symposium Report, 1:1, 1958.
2. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Archives Internal Med. 100:750, 1957.

* U. S. Patent 2,895,881

REFER TO PDR PAGE 867

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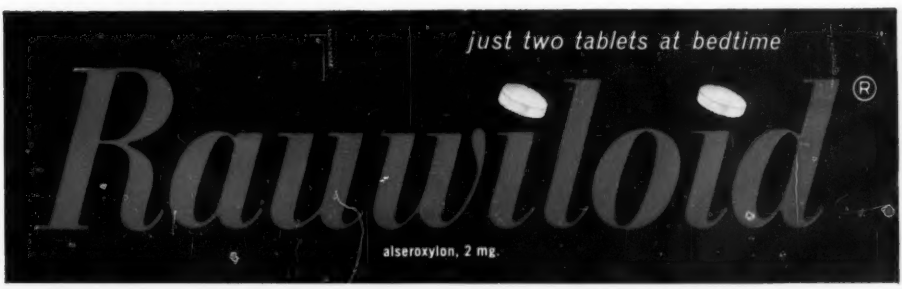

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